"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

FOLLOWING so soon after the increase of our Journal from four to six numbers per annum, our readers will be surprised that we have decided to bring it out each month. This will of necessity need an increase in subscription already somewhat overdue. So rapid are the changes that are taking place that new drugs made by chemists, tested by physiologists, are constantly being handed out to anaesthetists for trial. Techniques are becoming ever more complicated and their authors are anxious to get the papers describing them published at the earliest possible moment. On the one hand there is the very natural desire to be the pioneer of any epoch-making discovery and on the other the possibility that the matter will be out of date in three months time. Hitherto authors have had to wait sometimes almost a year before their papers appeared in print; that can hardly happen now. With this in mind we hope that more of our readers will become contributors and that the correspondence columns will be enlivened.

One subscriber who furnishes us with articles from time to time has welcomed the new arrangement so enthusiastically that he has sent us a poem presumably due to the exuberance of his spirit or merely to celebrate the monthly issue. Readers of modern poetry will be well aware that authors of such cannot get their contributions published unless (1) they are unintelligible; (2) the lines are of different lengths; (3) there are no rhymes. As our author failed in all these particulars we are unable to give our readers the opportunity of seeing his attempt.

ONE recalls that we were slightly shocked when Bailey, in 1941, stressed the necessity for a "regime" of treatment for cases of cardiac arrest. It seemed strange that one team should have such a large experience of such cases. Many must have thought " it could not happen to us ". Few, however, today would deny that Bailey's paper did, in fact, render a great service. By laying stress on the necessity of the rapid restoration of the circulation in cases of cardiac collapse, it has very probably saved many lives.

One might reasonably have hoped that the rapid strides made in anaesthesia would have reduced the incidence of cases of acute circulatory failure and collapse. The raising of the standard of education of specialist anaesthetists has, undoubtedly, played its part, and few of our patients suffer as a result of gross ignorance or misjudgment. But accidents still occasionally occur—a fact to which the investigation into anaesthetic deaths, carried out by the Association of Anaesthetists, is telling witness. Furthermore, more extensive and daring operations are being devised. The repair of lesions of, hitherto, " untouchable " organs, such as the heart, and this even in infants, who a few years ago would have been considered as impossible subjects for major surgical procedures, has introduced new problems. Among these problems is that of cardiac arrest and particularly that, hitherto, incurable variety, ventricular fibrillation. A recent annotation in the *Lancet* is evidence of the scope of the problem.

We welcome, therefore, the paper by Vetten *et al.* on page 2, which very properly stresses the importance of the rapid restoration of the coronary circulation and brings evidence to show that aortic occlusion increases the efficiency of cardiac massage.

REFERENCES

Bailey, H. (1941). *Brit. med. J.*, **2**, 84.
Annotation (1954). *Lancet*, **2**, 1217.

Brit. J. Anaesth. (1955), **27**, 2.

EXPERIMENTAL STUDIES IN CARDIAC MASSAGE WITH SPECIAL REFERENCE TO AORTIC OCCLUSION*

BY

K. BARBARA VETTEN, V. H. WILSON
G. R. CRAWSHAW, AND J. C. NICHOLSON

The Cardiac Surgical Research Unit, Department of Surgery, University of the Witwatersrand

CENTRAL circulatory failure is the gravest and most urgent complication with which one can be confronted on the operating table; treatment must be prompt and energetic to have any chance of success. The direct physiological approach of maintaining an artificial circulation by cardiac massage is the only logical procedure in such an emergency while the part played by drugs is controversial.

The chance of success with cardiac massage is greatest where the heart has been suddenly arrested in a patient whose general condition has been otherwise reasonably good. Where cardiac failure is secondary to shock, haemorrhage or toxaemia, a satisfactory response cannot be expected and senile or pathological degenerative changes in the cardiovascular system, especially the coronary arteries, are also unfavourable factors.

The urgency with which treatment must be instituted needs no repetition as it has been adequately emphasized by other writers, notably Hamilton Bailey (1941, 1947). The operating theatre provides the best opportunities for the successful treatment of cardiac failure, as it is only in such circumstances that the essential facilities are likely to be at hand. In assessing the value of cardiac massage, it must also be appreciated that only a small proportion of the cases where the heart fails on the operating table will respond favourably.

During the years 1950 to 1953 there were, in the Johannesburg Hospital, 32 cases of death on the operating table, covering 48,000 anaesthetics. Cardiac massage was carried out in 22 instances, but a detailed analysis showed that only in 3 were conditions apparently favourable. In a further 6, although the treatment was logical on clinical grounds, autopsy revealed gross cardiovascular pathology, while in the remaining 13 the outlook was hopeless from the start. In spite of this, however, the routine performance of cardiac massage, even when the chances of success are negligible, is a practice to be encouraged and the few successes have been extremely gratifying. Records show that this treatment is usually more regularly and promptly applied by surgeons who are accustomed to working in the abdomen or thorax. Failure in apparently favourable cases may be due to such factors as:

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(*a*) Delay in commencing the treatment.
(*b*) Inefficient methods of massage.
(*c*) Complicating factors, such as ventricular fibrillation, which may interfere with the re-establishment of normal cardiac rhythm.

THE PROBLEM OF CARDIAC ARREST

Cardiac asystole gives rise to anoxia in its most acute form, and the brain cells are the most sensitive to oxygen deprivation. In all too many cases, even when the heart has been successfully restarted, the patient only survives for a short time in the condition of a decerebrate animal. Mousel, Stubbs and Kreiselman (1946) found that complete cerebral anoxia for 10 seconds resulted in unconsciousness, 20 to 30 seconds caused cessation of electroencephalographic brain waves, and 3 to 5 minutes irreversible changes in the cerebrum. In a case of cardiac arrest, therefore, the first essential is to maintain a sufficient blood supply to the brain to prevent irreversible damage.

The myocardium, on the other hand, is extremely resistant to anoxia. By perfusing the coronary arteries, Kountz (1937) was able to restore normal rhythm in the hearts of individuals who had been clinically dead for periods up to 6 hours. None the less, in any scheme for resuscitation in cardiac failure, the coronary blood supply is extremely important as the re-establishment of a healthy spontaneous beat is a matter of urgency. Unlike the treatment of respiratory failure, where efficient pulmonary ventilation can easily be maintained for many hours, the best output obtainable by manually compressing the ventricles falls below normal requirements and, until a satisfactory spontaneous rhythm has been restored, a losing battle with anoxia is being fought. Stearns, Maison and Stutzman (1951) state that cardiac massage should maintain a mean arterial pressure of 40 to 60 mm. Hg, while Dripps and his co-workers (1948) give a figure of 60 to 70. Johnson and Kirby (1949) found that the rate of blood flow with cardiac massage was approximately half that produced by the spontaneous beat and that, after about 20 minutes, the aortic blood flow decreased significantly and the heart began to feel empty due, apparently, to inadequate diastolic filling. It would thus seem that, if a normal beat cannot be rapidly restored, there is grave danger of entering a vicious spiral of anoxia from which there is no escape. The best chance of saving the patient's life is, therefore, to restore normal rhythm as quickly as possible and, in the meantime, give the brain the best blood supply which can be made available. It is necessary to consider how to get the best results from manual compression of the heart; it would also appear logical to attempt, as far as possible, to concentrate the available output on the brain and coronary arteries.

The first to suggest the application of this principle was Wiggers (1940) who compressed the root of the aorta intermittently during cardiac massage in dogs, with the object of improving the coronary blood supply. Carter (1951) describes a case of cardiac massage, with complete recovery after 25 minutes, in which the aorta was compressed just beyond the left subclavian. Johnson and Kirby (1949), using the bubble meter of Dumke and Schmidt, studied the effect of cardiac

massage on the carotid blood flow of dogs; they found that the rate of flow in the carotid artery, during massage, was significantly increased by occluding the thoracic aorta.

OBJECTS AND METHODS OF INVESTIGATION

The paper describes one of a series of investigations into the haemodynamics of experimental mitral valve disease (Crawshaw, Vetten and Wilson, 1953; Wilson, Vetten, Crawshaw and Knocker, 1954), the ultimate purpose of the investigations being to explore the possibilities of reconstructive surgery in mitral incompetence. During the experiments, the most effective way of maintaining a satisfactory pressure in the carotid arteries of dogs undergoing cardiac massage was studied; this included both the best method of compressing the ventricles and the effect of occluding the aorta at points corresponding to sites which might be used clinically in the human subject in the event of cardiac arrest on the operating table. The most important of these points are:

(*a*) The thoracic aorta just distal to the left subclavian, a site readily available in thoracic procedures.

(*b*) The upper end of the abdominal aorta, including the coeliac axis, which is the highest point which could be used from an abdominal approach.

The cardiac arrests, which provided the opportunity of studying the effects of massage, were more often incidental than produced for the purpose of this investigation. This did not, however, interfere with the comparison of the occluded and unoccluded aorta and an opportunity of observing the effect of factors influencing the peripheral circulation was also provided.

Information has been collected in the course of experimental work on over 60 dogs, varying in weight from 30 to 90 lb. (13.6–40.8 kg.), during thoracotomy and experiments on hypothermia. Simultaneous electrocardiographic and pressure records from a systemic artery and venous sources in the left auricle and pulmonary veins have been made upon a Sanborne strain gauge amplifying recorder. Two of the amplifiers have been used to record tracings from high and low pressure sources through Statham physiological transducers. Direct recording has been made on Sanborne "Permpaper" at 25 mm. per second. The pressure recorders have been calibrated in mm. Hg against a mercury sphygmomanometer with air as the medium of transmission in the transducer system. During the animal experiments the pressure transmission has been through a column of heparinized normal saline in transparent polythene "Sterivac" catheters (Allen and Hanbury's) Size No. 3, into which a No. 15 Luer-Lok needle has been forced for attachment of the transducer. After cutting the polythene catheter, the tip has been rounded off by placing it in a current of warm air to remove sharpness without reducing the size of the lumen. Electrocardiographic changes have been recorded from needles inserted into the leg muscles of the animals. Electrical interference has been avoided by earthing the dog, the recording machine, and other electrical instruments.

The same surgeon, anaesthetist, and physician have been responsible for the

operative, anaesthetic, and recording procedures during all operations and experiments. Sodium pentobarbital has been used as the anaesthetic throughout (Crawshaw, Vetten and Wilson, 1953) to which has been added, in some of the experiments, various relaxants to suppress all respiratory movement. Atropine gr. 1/100 (0.65 mg.) was given in all cases. A wide-bore cuffed endotracheal tube was inserted and pulmonary ventilation maintained by intermittent inflation of the lungs with 100 per cent oxygen. In the hypothermic experiments "surface" refrigeration was used.

TECHNICAL ASPECTS OF CARDIAC MASSAGE

Approach.

Different methods of compressing the ventricles have been advocated. It is now generally accepted that subdiaphragmatic massage is unsatisfactory. It should only be employed as an initial measure and more effective methods instituted if the heart does not commence beating immediately. The transdiaphragmatic massage, advocated by Nicholson (1942), permits more efficient compression and can be used with minimum delay in abdominal procedures. There is, however, no doubt that the thoracic approach is the ideal. In our experiments it was found that by far the best results were obtained when the ventricles were encircled by the hand so that they could be compressed from all directions. This gives the nearest approach to the effect of a normally contracting myocardium but can only be carried out with an open thorax. Bonica (1952) stresses the value of the thoracic approach and recommends the use of transdiaphragmatic massage, as an interim measure, while thoracotomy is being performed. It is fortunate that it is in thoracic procedures that the occasion for cardiac massage is most likely to arise.

Rate.

Different rates of compression were tried. This aspect of cardiac massage has been studied by other workers and a considerable difference of opinion exists concerning the optimum rate (Johnson and Kirby, 1949; Stearns, Maison and Stutzman, 1951; Bonica, 1952). In our opinion this is largely governed by the venous return and hence the condition of the peripheral circulation. The more satisfactory the venous return the greater the rate of compression which can be used to advantage. The method of compression is more important than the rate, and rapid massage has a number of intrinsic disadvantages. Provided the condition of the peripheral vessels was good, tracings of rapid massage often showed high systolic "spikes", but the diastolic level was usually better maintained with the more sustained and progressive compressions which were only possible at slower rates. Figure 1, Dog 47, shows two carotid pressure tracings, which were taken in sequence so that there was no time for any appreciable change in the animal's condition. In (*a*) the heart was massaged at a rate of 50 per minute, and in (*b*) 120 per minute. The wider compression waves and better sustained diastolic pressure at the lower rate are clearly shown.

Rapid massage is very tiring to the operator and cannot be long sustained without relief. This is specially noticeable in large hearts as it is more difficult to

[continued on page 8

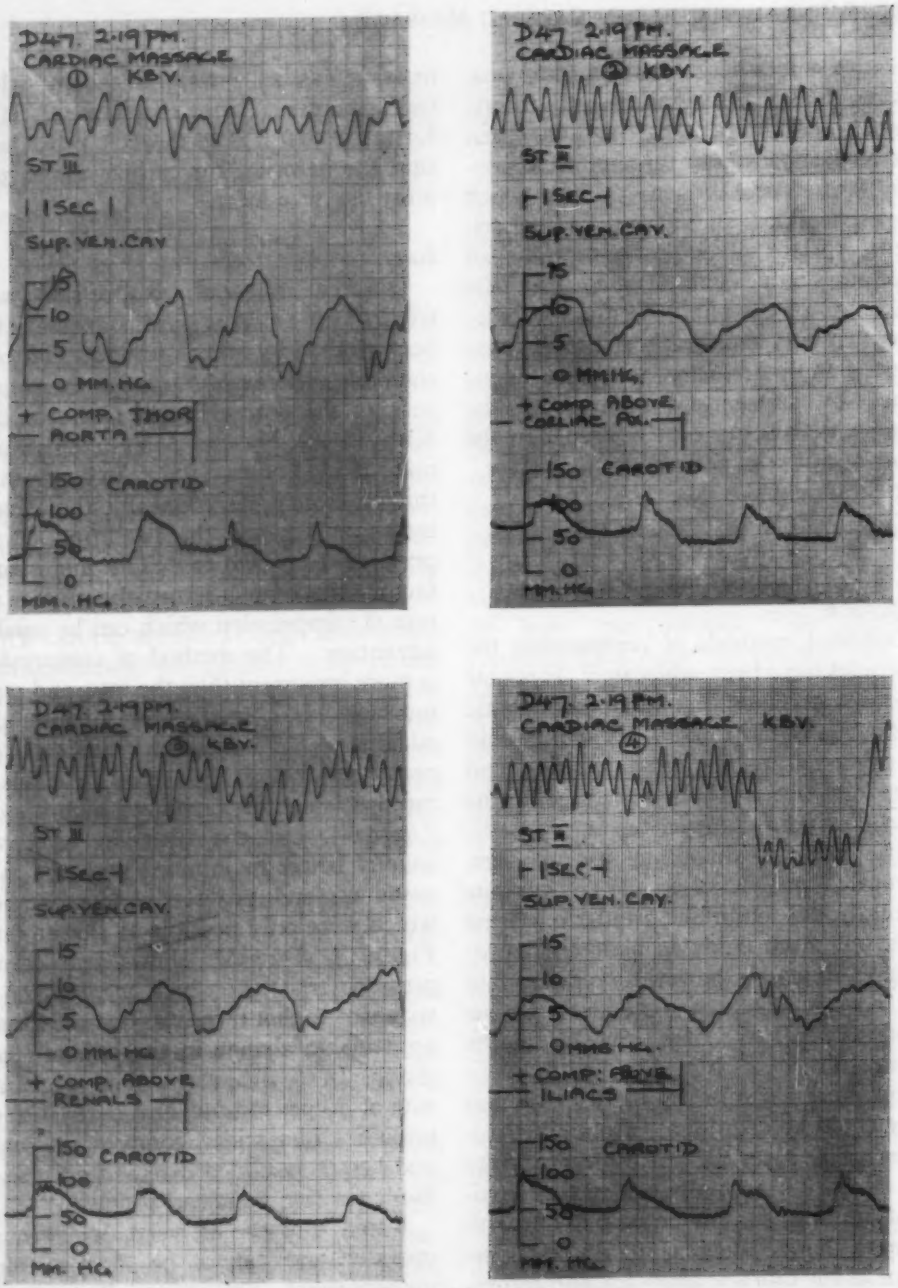

FIG. 1 (*a*)
Massage rate 50 per minute

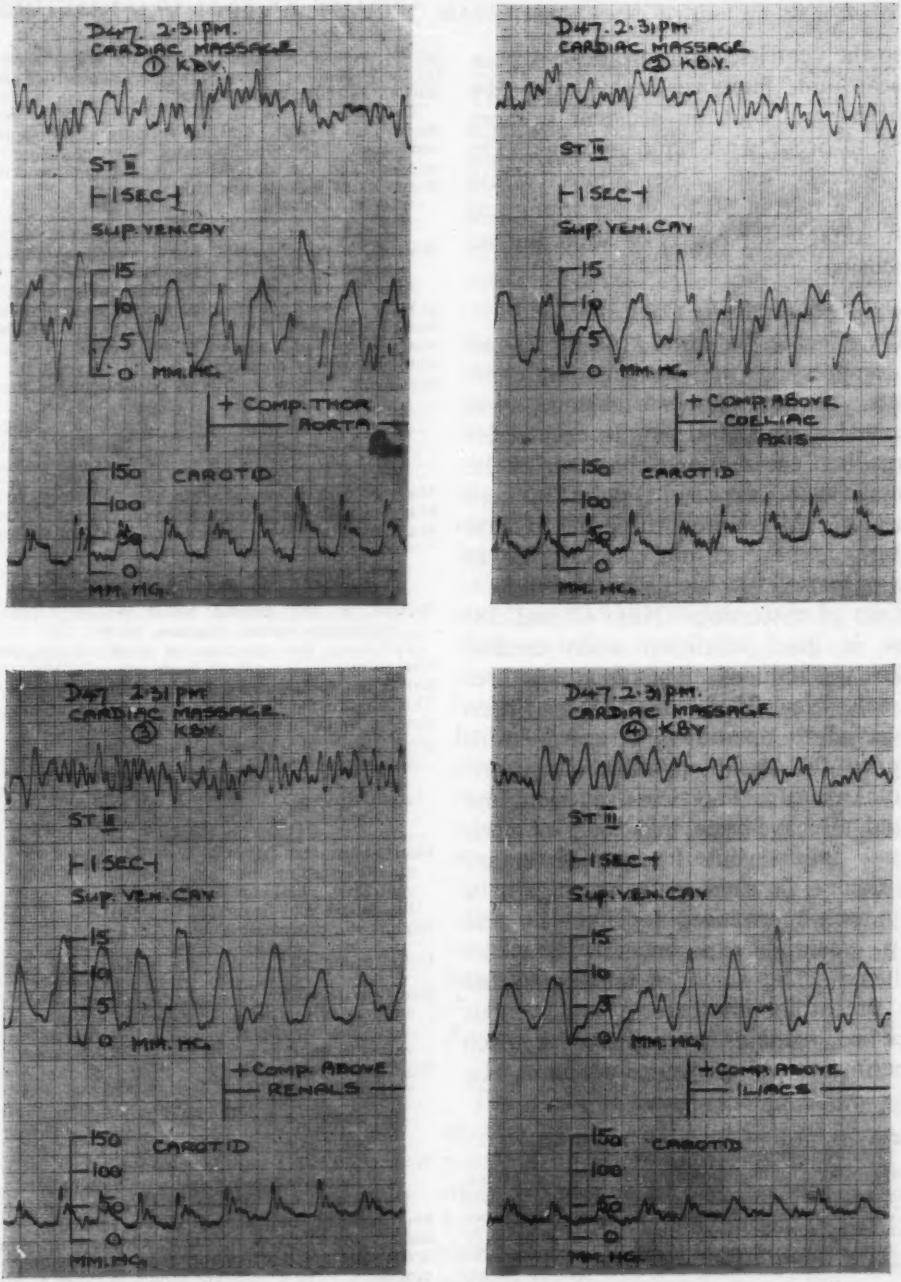

FIG. 1 (*b*)
Massage rate 120 per minute

grasp the ventricles comfortably. A poor myocardium, moreover, may easily be damaged and such an accident is more likely to occur with rapid massage. On the average our observations would suggest a rate of 50 to 60 per minute as most suitable for hearts of adult human dimensions.

The Effects of Aortic Occlusion.

The effect on the carotid blood pressure of compressing the aorta at different points, during cardiac massage, was observed in over 60 dogs. In each series of readings the rate and character of the massage was, as far as possible, kept constant. All showed the same general features and are set out, as examples, in five animals.

Two of these dogs (Nos. 47 and 58) were in good condition when cardiac failure was induced. The remaining three animals (Nos. 25, 31, and 35) had been subjected to operations of considerable severity for the production of experimental mitral and aortic valve lesions and would all have been in a state of peripheral failure but for supplementary infusions. To save space, tracings have only been reproduced for Dog 47, and only essential experimental data are included. The weight of the animal and the precardiotomy carotid and venous pressure readings are given for each experiment. All pressures are mm./Hg.

Dog 47

Weight, 41 lb.; carotid blood pressure, 150/125; pressure in superior vena cava, 3/−7.

Laparotomy and thoracotomy were performed, following which the carotid blood pressure dropped to 130/100. At this stage ventricular fibrillation, followed by complete cardiac arrest, was induced by the intravenous injection of 15 ml. KCl solution. The heart was then massaged, first at a rate of 50 per minute and then at a rate of 120 per minute. In each case the aorta was occluded at the following points: (*a*) the thoracic aorta, just beyond the left subclavian; (*b*) the abdominal aorta, above coeliac axis; (*c*) above renals; (*d*) above common iliacs.

The tracings show the effects of these occlusions on the carotid pressure, and the pressure in the superior vena cava. The line indicates where pressure was applied, and the stop where it was commenced or discontinued (figs. 1a and 1b).

Dog 58

Weight, 36 lb.; carotid blood pressure, 170/135; pressure in superior vena cava, 3/−3.

After thoracotomy the carotid pressure fell to 110/75. Ventricular fibrillation followed the intravenous injection of 700 mg. procaine amide. The heart was massaged at a rate of 85 per minute. The aorta was successively compressed (*a*) just beyond the left subclavian, and (*b*) as low as possible in the thorax.

	Carotid pressure	Superior vena cava pressure
Massage without compression	107/70	18/4
Massage with high compression	175/112	27/5
Massage with low compression	130/60	30/5

Dog 25

Weight, 55 lb.; carotid blood pressure, 150/125; pulmonary venous pressure, 16/5.

Following the induction of mitral incompetence, this animal had a severe haemorrhage. Ventricular fibrillation took place during suturing of the auricle. This was treated by cardiac massage and, at the same time, a rapid intravenous infusion of dextran was given. Rate of massage 120 per minute.

	Carotid pressures	Pulmonary venous pressures
Heart massaged for 1 minute grasping the ventricles between the thumb and fingers High aortic compression	100/40	40/10
Compression off	60/42	25/10
Heart massaged for 10 minutes fully encircling the ventricles with the hand High aortic compression reapplied	125/62	40/10

Dog 31

Weight, 49.5 lb.; carotid blood pressure, 165/125; pulmonary venous pressures, 3/−2.

This animal was the subject of experimental mitral and aortic incompetence. After induction of the lesions, the effect of occluding the aorta at different levels was noted while the heart was beating spontaneously. The results are shown in table A. Ventricular fibrillation was then induced by occluding the coronary arteries and cardiac massage, at a rate of

70 per minute, immediately commenced. Table B shows the results of occluding the aorta during massage for comparison with the spontaneous beat.

TABLE A

	Carotid pressures	Pulmonary venous pressures
Controls after induction of valvular lesions	120/50	15/−5
Aorta clamped below renals	125/50	15/0
Aorta clamped above renals	150/78	25/3
High occlusion of thoracic aorta	195/90	50/0

TABLE B

	Carotid pressures	Pulmonary venous pressures
Cardiac massage alone	50/10	15/4
Massage with high occlusion of thoracic aorta	100/10	25/5
Massage with occlusion of abdominal aorta above coeliac axis	56/10	22/4

The pressures obtainable by cardiac massage were less than half those shown with the spontaneous beat. The animal's condition was deteriorating rapidly, and the exceptionally low diastolic pressures were probably the result of the experimental aortic lesion.

Dog 35

Weight 72 lb.; carotid blood pressure, 165/125; pulmonary venous pressure, 4/0.

This animal was the subject of experimental mitral incompetence. Ventricular fibrillation followed a severe haemorrhage. Rapid intravenous autotransfusion was given. Cardiac massage, at a rate of 60 per minute, was instituted.

	Carotid pressures	Pulmonary venous pressures
Cardiac massage alone	54/25	25/0
With occlusion of abdominal aorta above coeliac axis	75/24	20/0
With high aortic occlusion	100/25	25/10
Cardiac massage alone—compression off	50/15	5/0

This animal was in a condition of advanced peripheral circulatory failure.

These experiments show that compression of the aorta, during cardiac massage, results in a marked increase in the carotid pressure. In most cases both systolic and diastolic pressures rose, but the effect on the systolic was usually more pronounced. The rise in pressure was usually greater when the aorta was compressed at higher levels, but a few animals (e.g., Dog 47) showed a lower diastolic reading with high aortic occlusion than with occlusion at lower levels. Although the *systolic* pressure was almost invariably improved by clamping the aorta, in a fair proportion of the dogs there was no very marked increase in *diastolic* pressure. It seems quite probable that high clamping of the aorta may sometimes interfere with the venous return and lead to inadequate diastolic filling. Other writers have recommended the use of intravenous or intra-arterial infusions during cardiac massage (Alexander and Hewer, 1952; Stevenson and Hinton, 1953; Wilson, Vetten, Crawshaw and Knocker, 1954), and our own observations support the view that this forms an important part of the treatment. In this respect, however, the raised pulmonary venous and right auricular pressures must also be regarded as of serious significance for they suggest a strong tendency to pulmonary oedema and, while vigorous treatment by infusion is of great value in helping to maintain the cardiac output, it will certainly aggravate the latter complication.

Factors Influencing the Peripheral Circulation.

The effect of hexamethonium bromide on the carotid and pulmonary venous pressures, during cardiac massage, was studied in three dogs (Nos. 36, 32, and 33). In a further two animals (Nos. 27 and 8) similar observations were made when ventricular fibrillation occurred following refrigeration.

Dog 36

Weight, 63 lb.; carotid blood pressure, 160/125; pulmonary venous pressure, 5/−2.

Following thoracotomy the blood pressure fell to 125/100, and the administration of 100 mg. of hexamethonium bromide caused a further fall to 100/60. About 20 minutes later the heart went into ventricular fibrillation. Cardiac massage was carried out at about 30 per minute (diastolic filling being insufficient for faster rhythm). The response of the carotid pressure was barely perceptible. Aortic compression produced a slight improvement, but not sufficient to be of any therapeutic significance.

Figure 2 shows carotid and pulmonary pressure tracings:

(*a*) Heart beating spontaneously before administration of hexamethonium.

(*b*) Heart beating spontaneously after administration of hexamethonium.

(*c*) Cardiac massage without occlusion.

(*d*) Cardiac massage with high aortic occlusion.

Dog 32

Weight, 60 lb.; carotid blood pressure, 150/100; pulmonary venous pressure, 3/−3.

This dog was the subject of an experiment for the creation and study of mitral and aortic incompetence. During the procedure there was a gross haemorrhage which the operator found difficulty in controlling. Hexamethonium bromide 100 mg. was administered, causing the carotid blood pressure to fall to 25/22. This did not stop the haemorrhage but ventricular fibrillation supervened. Cardiac massage produced no perceptible response in carotid blood pressure and high thoracic occlusion of the aorta was also without effect.

	Carotid pressures	Pulmonary venous pressures
Before haemorrhage (spontaneous beat)	125/90	10/0
After haemorrhage (spontaneous beat)	52/25	3/−3
After pooling blood with hexamethonium bromide (fibrillation at this stage)	25/22	4/0
Cardiac massage with high aortic occlusion	25/22	10/0

Dog 33

Weight, 31 lb.; carotid blood pressure, 150/120; pulmonary venous pressure, 3/−3.

Operation for the production of experimental mitral and aortic incompetence. Carotid pressure after thoracotomy was 130/105. Hexamethonium bromide 25 mg. was administered fractionally in 5-mg. doses following which the carotid pressure fell to 50/25 and afterwards ventricular fibrillation supervened. Cardiac massage was carried out at a rate of 60 per minute, at first alone and later with occlusion of the thoracic aorta.

	Carotid pressures	Pulmonary venous pressures
Cardiac massage without occlusion	55/40	30/10
Cardiac massage with occlusion of thoracic aorta	72/50	30/10

Dog 8

Weight, 52.5 lb.; arterial blood pressure (recorded from femoral), 200/150.

This animal was the subject of a refrigeration experiment and, apart from the insertion of the femoral catheter, there was no surgical interference up to the time of cardiac failure. When the rectal temperature was reduced to 25°C. the blood pressure fell to 125/75. At this point ventricular fibrillation supervened. Thoracotomy was rapidly performed and cardiac massage at about 50 per minute was carried out. The maximum systolic pressure attained in the femoral artery was only 26, and no diastolic reading was recordable. Pulmonary venous pressures were not taken.

Dog 27

Weight, 40 lb.; carotid blood pressure, 130/100; pulmonary venous pressure, 5/−1.

Subject of investigation of experimental mitral and aortic incompetence and was operated on under refrigeration. There was no unusual haemorrhage or trauma associated with the procedure.

Rectal temperature	Carotid pressure	Pulmonary venous pressure
30°C.	130/100	5/0
24.5°C.	60/40	12/5

At the lower temperature, ventricular fibrillation occurred and cardiac massage was commenced. Massage with high aortic compression only raised the carotid pressure to 50/8, the pulmonary venous reading being 9/4.

When peripheral vasodilatation and pooling of blood in the capillaries were produced by the use of hexamethonium bromide, the response to cardiac massage, irrespective of whether the aorta was occluded or not, was very poor. A similar

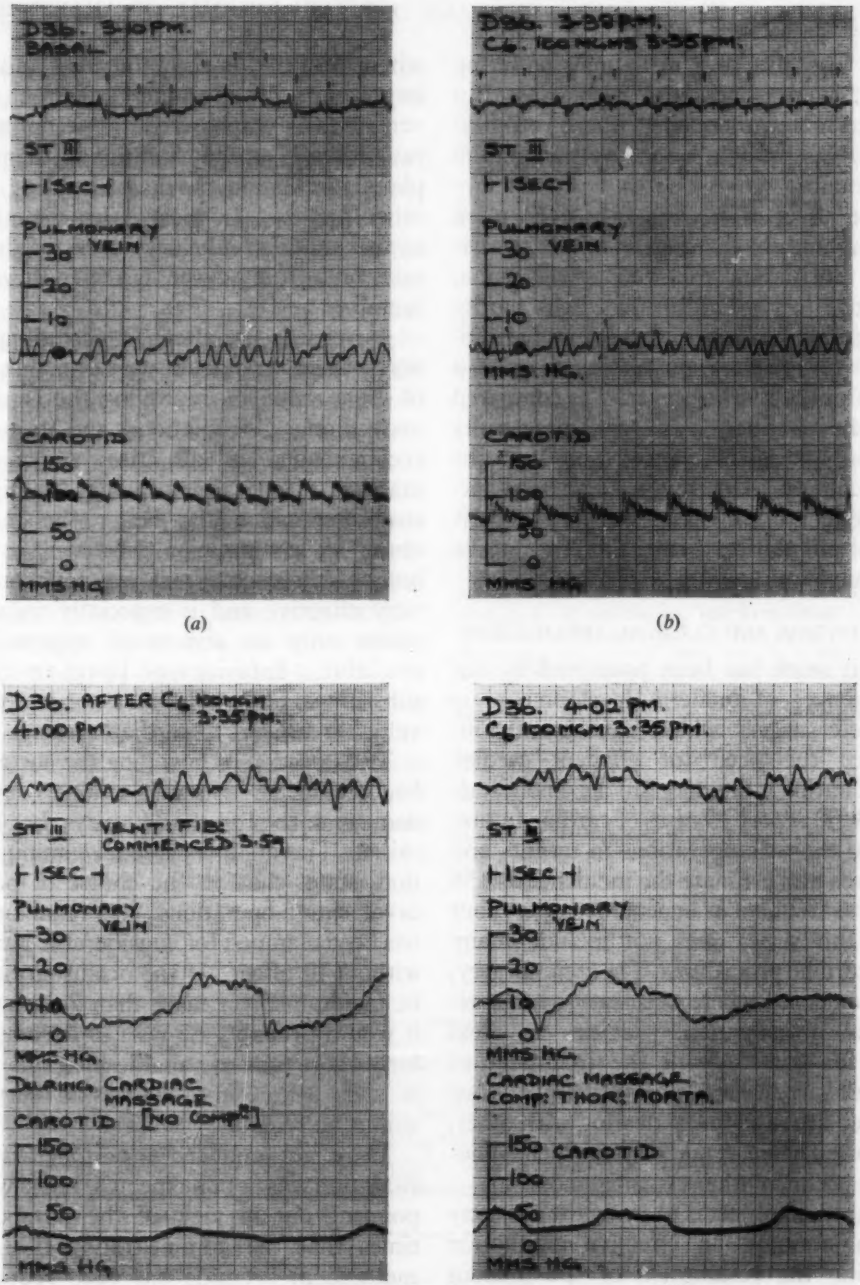

FIG. 2

Before and after hexamethonium bromide.

effect was also seen in animals suffering from severe shock and blood loss but seemed more pronounced where vasodilatation was brought about by methonium compounds.

The effect of freezing was even more striking and, in the dogs in which ventricular fibrillation followed refrigeration, response to cardiac massage was hardly perceptible. Neither of the animals subjected to refrigeration had undergone a procedure of marked severity as compared with the other dogs. In Dog 8, practically the only surgical intervention was the thoracotomy to permit cardiac massage. The effect of refrigeration on the peripheral circulation seems, therefore, to be profound.

DISCUSSION AND CLINICAL APPLICATION

This work has been prompted by our experiences of modern developments in thoracic surgery which have greatly increased the need for efficient cardiac resuscitation. Snyder, Snyder and Chaffin (1953) report 35 cases of cardiac failure in 550 thoracic operations in infants and children and estimate the incidence as 156 times as frequent as in general surgery, but even this series does not include many intracardiac procedures. Thoracic surgery, supplemented where necessary by experimental investigation, provides an ideal field for the study of the treatment of cardiac arrest and any principles thus learned are of value in dealing with other, and often more tragic, cases which sometimes occur in other circumstances.

The main object is to study the best way of maintaining an effective circulation pending the resumption of spontaneous heart action. The thoracic approach, where possible, is recommended and the importance of adequately grasping the ventricles is emphasized. The optimum rate depends on the condition of the peripheral circulation, the diastolic filling, and other factors. In most cases something approximating to the normal resting heart rate, or a little slower, is the most satisfactory.

As regards the effect of occluding the aorta, there is no doubt whatever that it is of great value in improving the cerebral and coronary circulations, and its use is recommended in all cases of cardiac massage. Generally speaking, the higher the compression the better the results obtained; compression, however, at the level of the coeliac axis was found to be very effective and is especially valuable where only an abdominal approach is available. Infusions of blood or blood substitutes, preferably intra-aortic, form a valuable adjunct to cardiac massage.

The question of how long the aorta can be occluded, without risking serious damage to the liver and kidneys, has been raised. Theron, in a personal communication, states that, in the course of porta-caval shunt operations, the renal artery has been clamped for considerable periods without ill effect. If the occlusion has to be maintained for more than 20 minutes, it would probably be wise to decompress for a short time at suitable intervals, but, in such a case the chances of survival would be remote.

The effect produced by peripheral vasodilatation was not unexpected, but is worth pointing out in view of the number of times that the administration of hexamethonium bromide has been requested by surgeons as a treatment for serious

haemorrhage; such a step should never be taken without a full realization of its implications.

The problem of restarting the heart only comes within the scope of this paper in so far as massage itself frequently initiates a spontaneous beat, but it is the all-important issue. The writers do not agree with Cole (1952) who considers that once cardiac massage has been started the emergency ceases to exist; on the contrary it cannot stave off the onset of peripheral circulatory failure for very long and while supportive infusions may help for a time they also increase the liability to pulmonary oedema. This pulmonary oedema is a very grave danger and was an important factor in many of the experimental animals. The key to success in cardiac resuscitation is to re-establish a spontaneous beat as soon as possible.

The control of cardiac action during thoracotomy in general, and left ventricular cardiotomy in particular, is at present being studied and will be the subject of a later paper which will be complementary to this communication.

ACKNOWLEDGMENTS

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REFERENCES

Alexander, L., and Hewer, C. Langton (1952). *Brit. med. J.*, **2**, 546.
Bailey, Hamilton (1941). *Brit. med. J.*, **2**, 84.
—— (1947). *Lancet*, **1**, 5.
Bonica, J. (1952). *Curr. Res. Anesth.*, **31**, 1.
Carter, M. G. (1951). *J. Amer. med. Ass.*, **147**, 14.
Cole, F. (1952). *Arch. Surg., Chicago*, **64**, 2.
Crawshaw, G. R., Vetten, K. B., and Wilson, V. H. (1953). *S. Afr. J. med. Sci.*, **18**, 79.
Dripps, R. D., Kirby, C. K., Johnson, J., and Erb, W. H. (1948). *Ann. Surg.*, **127**, 592.
Johnson, J., and Kirby, C. K. (1949). *Surgery*, **26**, 472.
Kountz, W. B. (1937). *Ann. intern. Med.*, **10**, 330.
Mousel, L. H., Stubbs, D., and Kreiselman, J. (1946). *Anesthesiology*, **7**, 1.
Nicholson, J. C. (1942). *Brit. med. J.*, **1**, 385.
Snyder, W. H., Snyder, M. H., and Chaffin, L. (1953). *Arch. Surg., Chicago*, **66**, 6.
Stearns, N. S., Maison, G. L., and Stutzman, J. W. (1951). *Amer. J. Physiol.*, **164**, 601.
Stevenson, H. E., and Hinton, J. W. (1953). *J. Amer. med. Ass.*, **125**, 6.
Theron, P. Personal communication.
Wiggers, Carl J. (1940). *Amer. Heart J.*, **20**, 413.
Wilson, V. H., Vetten, K. B., Crawshaw, G. R., and Knocker, P. (1954). *S. Afr. J. med. Sci.*, **19**, 1.

In the November issue of the *Journal*, at the head of the article "Anaesthesia for Intra-Nasal and Intra-Oral Operations in Adults" (page 418), the address of the author is shown as "*Bradford* Group of Hospitals". This should have read "*Bedford* Group of Hospitals". Since the publication of the above, however, the address of Dr. E. Harvey Franks has been changed to Department of Anaesthetics, Cardiff Royal Infirmary, to which address all communications should now be sent.

Brit. J. Anaesth. (1955), **27**, 14.

THIOPENTONE AS A FACTOR IN THE PRODUCTION OF LIVER DYSFUNCTION

BY

JOHN W. DUNDEE

Department of Anaesthesia, University of Liverpool

AFTER a long controversy there is now abundant evidence to show that the liver is the main site of detoxication of thiopentone. This applies both to animals (Walker and Wynn Parry, 1949; Gould and Shideman, 1952; Shideman, Gould, Winters, Peterson and Wilner, 1953; Meyers and Peoples, 1954) and man (Shideman, Kelly, Lee, Lovell and Adams, 1949; Dundee, 1952). Furthermore it is now established that detoxication of thiopentone is a slow process, only 10–15 per cent of the drug in the body being metabolized per hour (Brodie, Mark, Papper, Lief, Bernstein and Rovenstine, 1950; Brodie, Bernstein and Mark, 1952). One might expect the drug to have a toxic action on the liver, but there is no definite evidence for this in man.

Richards and Appel (1941) have shown that hepatic impairment follows the use of thiopentone in animals. The smaller the animal the more marked was the effect of the drug on the liver. Walton, Uhl, Egner and Livingstone (1950) found that small doses of thiopentone were mildly toxic to both the normal and damaged liver of the dog, but this effect was due to hypoxia and could be overcome by adequate ventilation with oxygen. Doses of 20 mg./kg. given twice daily to normal dogs for periods of 2–3 weeks caused a mild depression of hepatic function, as judged by prothrombin time and serum bilirubin level, with complete return to normal four days after the last injection of thiopentone (Walton, Saldamando and Egner, 1951). In contradistinction to the effects of small doses, adequate oxygenation did not reduce the toxicity of repeated large doses of thiopentone.

Pohle (1948), using a battery of liver function tests found that liver impairment occurred in 50 per cent of cases after operation. Its occurrence was unrelated to the anaesthetic agent used, and the effects of thiopentone did not differ from those of chloroform. Unfortunately, the doses of barbiturate used were not recorded. The patients he studied were in poor general condition before operation and he suggested that their nutritional state and the occurrence of hypoxia after operation were the important factors in the aetiology of liver damage. Fairlie, Barso, French, Jones and Beecher (1951) examined the effects of anaesthetics (excluding thiopentone) and also found no significant difference in the effects of the various agents on the liver.

Carraway (1939), using the hippuric acid excretion test, found no alteration in liver function after thiopentone in 100 cases. Many of these patients were

jaundiced or had liver damage before operation. Using the same test, Boyce and McFetridge (1938a) found that ether, ethylene and spinal analgesia all had a marked effect on liver function for the first seven days after operation. The hippuric acid excretion test, urobilinogen metabolism, and blood sugar levels were examined by Mordvinova (1948) before and after thiopentone anaesthesia in 80 cases. The detoxicating function was significantly lowered in 17 patients, pigment metabolism was upset in 31 cases and blood sugar levels were abnormal in 17 cases. Recovery to normal took as long as two weeks in some instances. A much quoted case, reported by Vaizey (1928), describes the occurrence of jaundice following thiopentone, but the evidence incriminating the drug is not very convincing.

It can be seen from the above that there is no agreement as to the hepato-toxic properties of thiopentone. In this paper the effects of large and small doses of the drug on liver function are reported in 464 patients. No comparison is made between the effects of thiopentone and other anaesthetic agents. The urinary excretion of urobilinogen has been used to detect hepatic dysfunction in this series. Because of the pitfalls in the use and interpretation of the results of this test the metabolism of urobilinogen and factors influencing it will first be described in detail.

UROBILINOGEN EXCRETION

Normal Excretion.

Bilirubin that enters the intestine in the bile undergoes reduction by bacteria to form stercobilinogen (urobilinogen). A part of this is excreted in the faeces as urobilin. The remainder is reabsorbed into the portal circulation, passes through the liver and is almost completely re-excreted in the bile. Any urobilinogen which may escape into the circulation is excreted by the kidneys. Normally no urobilinogen (or a mere trace) appears in the urine.

Factors Influencing Excretion.

1. *Increased production of bilirubin.*

(*a*) Extravasation of blood. Elton (1931, 1950) has shown that "post-operative latent jaundice" occurs following contusions, fractures, lacerations, operation incisions, etc. An excess of bilirubin is formed and released into the blood stream to be excreted by the liver. Even though liver function is normal, it is unable to re-excrete the excess pigment absorbed from the intestine, and urobilinogen appears in the urine.

(*b*) Opinions vary as to whether the products of intravascular haemolysis are converted to urobilinogen. Harrison (1947) lists excessive haemolysis as a cause of urobilinuria. Fairley (1941) states that methaemoglobin occurs in the plasma following intravascular haemolysis and is excreted mostly as faecal porphyrin.

(*c*) Pernicious Anaemia.

2. *Liver Dysfunction.* Failure of the liver to re-excrete the absorbed urobilinogen results in an increase in the amount of absorbed urobilinogen excreted by the kidneys. Glynn (1949) considers a rise in urinary urobilinogen to be a sensitive test of liver function, frequently preceding any demonstrable retention of bile pigment in parenchymatous hepatitis. In a correlation of morphological liver changes and clinical tests Popper, Steigmann and Szanto (1949) found that an increase in urinary urobilinogen excretion bore closer relation to the results of liver biopsy than any of the other liver function tests investigated. The test is of no value in assessing the degree of liver damage present. They conclude that a positive cephalin-cholesterol flocculation test together with an increased urinary urobilinogen excretion indicates liver cell damage, while negative results do not exclude it in the presence of biliary obstruction.

3. *Obstruction of the common bile duct.* At first there is an accumulation of urobilinogen in the blood with resultant excretion in the urine. This can only occur for a short time after obstruction of the flow of bile, and is due to absorption of the pigment remaining in the intestine from the period prior to the obstruction. After this pigment has been removed urinary urobilinogen excretion completely ceases.

4. *Constipation* offers increased opportunity for absorption of urobilinogen from the large intestine with a consequent increase in urinary excretion.

5. *Most fevers* are accompanied by an increased urinary excretion of urobilinogen, probably due to temporary cloudy swelling of the liver.

METHOD OF INVESTIGATION

From the preceding discussion it can be seen that urobilinogen excretion in the urine cannot be utilized to assess the effect of anaesthetic agents on liver function in man unless the drugs be administered to volunteer subjects who undergo no operative procedures. The absorption of extravasated blood and post-operative consti-

pation or pyrexia are factors which of themselves could increase excretion of the pigment irrespective of liver function.

However, it can be used to compare the effects of different agents, or different doses of the same agent, in subjects undergoing the same operative procedure. In a large enough series of cases it can be hoped that the effect of the operative procedure and its sequelae will be the same with each agent under study. This is the basis of the present investigation.

The concentration of urobilinogen in the urine was measured for three days after operation in two series of cases. In one series thiopentone was the main narcotic, supplemented by nitrous oxide, muscle relaxants or minimal doses of other agents as required. In the other cases thiopentone was used only for induction of anaesthesia and followed by the usual doses of other agents. Details of the patients, operations and anaesthetic techniques in each series are shown in table I. This shows that both series are comparable with the exception of the anaesthetic agents. Since age may be a factor in making the liver more susceptible to the effects of thiopentone, the age distribution of each series is shown in greater detail in figure 1. This shows no appreciable difference between the patients to whom thiopentone was administered as the main anaesthetic agent and those who received it only for the induction of anaesthesia.

In each operation group both series of cases were from the same surgical unit in the same hospital. This ensured the same pre-operative preparation, the same premedication: morphine 1/6 gr. (10 mg.) and atropine 1/100 gr. (0.65 mg.) were given to each patient. The same post-operative routine was followed for all patients having the same operation. No patients were included who received any intravenous infusions or transfusions during operation, or in whom there was any prolonged (10 mins.) blood pressure fall. There was no restriction of analgesics or sedatives after operation, each patient receiving the routine drug for the ward. Any patient who developed a pyrexia (over 99.5°F.) or any other complication during the first three days after operation was excluded from the series. The majority of anaesthetics were personally administered.

It was originally proposed to do a quantitative estimation of urobilinogen on 24-hour specimens of urine for the first three days after operation. The loss of one sample of urine meant that the case had to be discarded and in the patients listed in table I, the concentration of urobilinogen was estimated in one sample of urine voided as near as possible to 20, 44 and 68 hours after operation using the technique described by Harrison (1947).

It will be noted that urobilinogen estimations were not carried out as a routine before operation. This was done in the early cases, but it soon became obvious that abnormal concentrations did not appear during the first 24 hours after operation. This can be accounted for by the time taken for absorption and re-excretion of the pigment. Any pre-operative abnormality was detected in the 24-hour specimen of urine. Patients who showed an excess of urobilinogen on the first post-operative day were excluded from the series.

As has been mentioned previously, there is some doubt as to whether intra-

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Appendicect	
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Plastic opera	
Haemorrhoi	
For hydrocel	
Hysterectom	
Thyroidector	
Incisional he	
Meniscectom	
Totals	...

TABLE

Details of 464 patients, nature and duration of operations and anaesthetic techniques, in

A. 232 cases in which thiopentone

B. 232 cases in which thiopentone

Operations	No. of cases in each series	DETAILS OF PATIENTS											
		Average age (years)		Sex distribution				Average duration of operations (mins.)		Average dose of thiopentone (G)		Gaseous	
				Males		Females						Nitrous oxide	
		A	B	A	B	A	B	A	B	A	B	A	
Dilatation and curettage ...	84	38.0	34.0	—	—	84	84	15.3	15.1	1.08	0.42	77	
Inguinal hernia repair ...	44	44.7	42.4	36	32	8	12	60.8	48.1	1.47	0.46	44	
Varicose vein ligation ...	18	35.9	35.9	11	12	7	6	56.7	56.6	1.36	0.48	17	
Appendicectomy	15	33.5	35.7	9	11	6	4	33.0	30.0	1.02	0.44	15	
Lumbar sympathectomy	13	44.9	45.1	7	5	6	8	67.7	63.5	0.87	0.52	13	
Plastic operations	11	41.7	31.8	5	3	6	8	45.5	37.3	1.10	0.42	11	
Haemorrhoidectomy ...	11	41.1	43.2	8	8	3	3	25.0	23.6	1.08	0.49	11	
For hydrocele	10	46.5	40.1	10	10	—	—	44.0	52.0	1.03	0.46	10	
Hysterectomy	9	46.8	47.6	—	—	9	9	65.0	77.8	1.19	0.46	9	
Thyroidectomy	8	37.1	35.0	2	2	6	6	48.0	75.6	0.99	0.38	8	
Incisional hernia repair ...	6	49.3	48.8	6	6	0	0	100.8	85.0	1.23	0.40	5	
Meniscectomy	3	32.7	47.7	3	3	0	0	40.0	26.7	1.75	0.43	3	
Totals	232	40.4	38.3	97	92	135	140	40.0	37.7	1.17	0.44	223	18

TABLE I

ic techniques, in whom urinary urobilinogen concentration was measured for three days after operation.
ch thiopentone was the main anaesthetic agent.
h thiopentone was only used for induction of anaesthesia.

DETAILS OF ANAESTHETICS

se of (G)	Gaseous supplements				Volatile supplements								Muscle relaxants				
	Nitrous oxide		Cyclopropane		Diethyl-ether		Trichlor-ethylene		Methyl-n-propyl ether		Pethidine		d-Tubocurarine chloride		Gallamine triethiodide		Suxa
B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
0.42	77	57	2	24	0	49	1	1	2	11	0	0	—	—	—	—	—
0.46	44	37	0	7	2	30	2	6	0	0	2	2	13	8	26	9	4
0.48	17	15	0	1	0	9	2	6	0	2	1	5	—	—	—	—	—
0.44	15	13	0	2	1	3	0	2	—	—	—	—	2	1	8	3	4
0.52	13	12	0	1	0	1	—	—	—	—	1	6	11	13	2	0	—
0.42	11	11	0	0	0	4	3	7	—	—	1	2	—	—	4	4	2
0.49	11	11	0	0	2	10	1	1	—	—	—	—	—	—	8	3	1
0.46	10	9	0	1	—	5	2	5	—	—	1	2	—	—	—	—	—
0.46	9	9	0	0	1	9	—	—	—	—	2	1	6	8	3	1	—
0.38	8	8	0	0	1	5	1	3	0	1	1	2	—	—	4	1	3
0.40	5	4	1	2	0	5	0	1	—	—	3	2	6	6	6	6	—
0.43	3	3	0	0	0	1	0	1	—	—	0*	1	—	—	—	—	—
0.44	223	189	3	38	7	137	12	33	2	14	12	23	32	30	61	27	14

[facin

nts

e	Suxamethonium	
B	A	B
-	—	—
9	4	2
-	—	—
3	4	0
9	—	—
4	2	3
3	1	1
-	—	—
1	—	—
1	3	3
-	—	—
-	—	—
7	14	9

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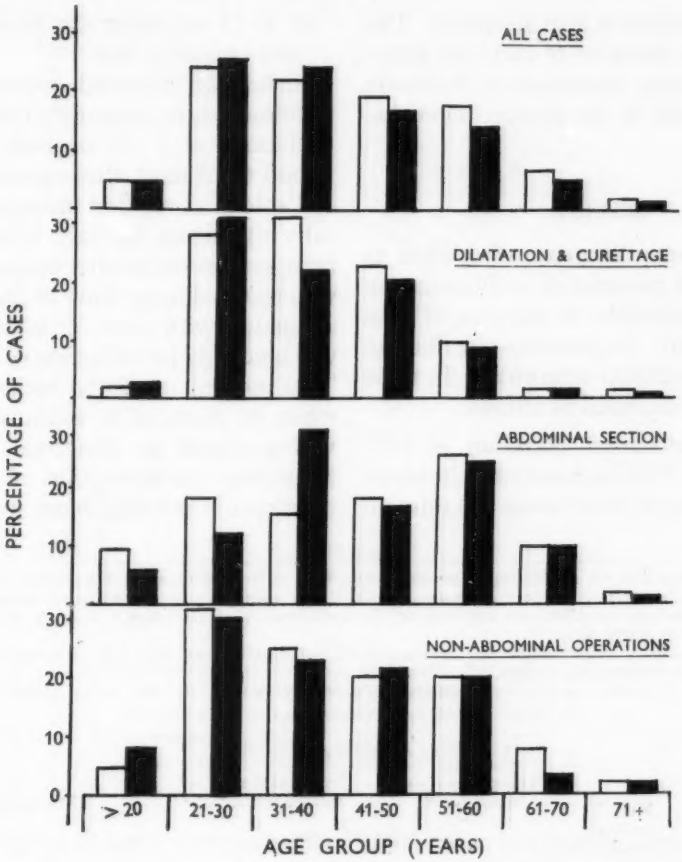

FIG. 1

Histograms showing the age distribution in the two series of patients described in test.

□ patients who received large doses of thiopentone.

■ patients to whom the drug was given only for induction of anaesthesia.

vascular haemolysis results in an increased urinary excretion of urobilinogen. To ascertain what part intravascular haemolysis played in the results obtained its presence was looked for in 40 cases. These include both patients with normal and excess urinary urobilinogen excretion and those receiving large and small doses of thiopentone.

The method used for detection of intravascular haemolysis is based on the observation that the presence of carbonic anhydrase in the urine indicates intravascular destruction of erythrocytes (Robinson, 1950). Where extravascular haemolysis has occurred the erythrocytes are destroyed within the cells of the reticulo-endothelial system and their

carbonic anhydrase is also destroyed. The technique for detection of carbonic anhydrase in the urine described by Robinson (1950) was used in the present investigation.

RESULTS

There is some difference of opinion as to whether the presence of urobilinogen in the urine, detectable in dilutions of 1 in 15, is abnormal. Its presence to a dilution of 1 : 20 is definitely abnormal. In table II results are recorded as follows:

± possibly increased excretion of urobilinogen. This includes cases in whom it was detected in the urine in a dilution of 1 : 15 on either the second or third post-operative day.

\+ definitely increased excretion of urobilinogen, its presence in the urine to a dilution of 1 : 20 on both the second and third days after operation.

Table II shows that there was a statistically significant increase in urinary urobilinogen excretion after operation in cases who received large doses of thiopentone as compared with those in whom the drug was used only for induction of anaesthesia. This applied to all the operation groups when its presence to a dilution of 1 : 15 was accepted as abnormal. With the alternative interpretation of results the difference is not significant in the patients

TABLE II

Post-operative excretion of urobilinogen in 464 cases, half of whom received thiopentone as the main anaesthetic agent; in the remaining half it was used only as an induction agent.

\+ *signifies that urinary urobilinogen was detected in a dilution of greater than 1 in 20 in the second and third post-operative days.*

± *signifies that urinary urobilinogen was detected in a dilution of greater than 1 in 15 in either the second or the third post-operative days.*

p *probability of difference in urinary urobilinogen excretion between the two series having occurred by chance.*

Operation	No. of cases in each series	Post-operative urobilinogen excretion: Thiopentone as main agent — Number of cases			Thiopentone for induction only — Number of cases			Difference between series: + χ^2	+ p	± χ^2	± p
		+	±	−	+	±	−				
Dilatation and curettage	84	20	44	40	5	6	78	259.2	<.001	47.9	<.001
Inguinal hernia repair	44	28	36	8	7	9	35	101.8	<.001	74.9	<.001
Varicose vein ligation	18	5	14	4	0	1	17	178.9	<.001	26.4	<.001
Appendicectomy	15	7	12	3	4	4	11	21.8	<.001	3.1	<.05 >.01
Lumbar sympathectomy	13	8	10	3	3	3	10	23.3	<.001	10.4	<.01
Plastic operations	11	7	10	1	1	1	10	89.1	<.001	39.6	<.001
Haemorrhoidectomy	11	8	11	0	3	4	7	17.3	<.001	11.5	<.001
For hydrocele	10	8	8	2	0	0	10	70.4	<.001	70.4	<.001
Hysterectomy	9	6	7	2	0	0	9	54.4	<.001	40.0	<.001
Thyroidectomy	8	4	8	0	2	2	6	24.0	<.001	2.7	<.2 >.1
Incisional hernia repair	6	3	4	2	0	0	6	18.7	<.001	10.7	<.01
Meniscectomy	3	1	2	1	0	0	3	5.3	<.05	1.3	<.3 >.2
TOTALS	232	105	166	66	25	30	202	708.1	<.001	286.9	<.001

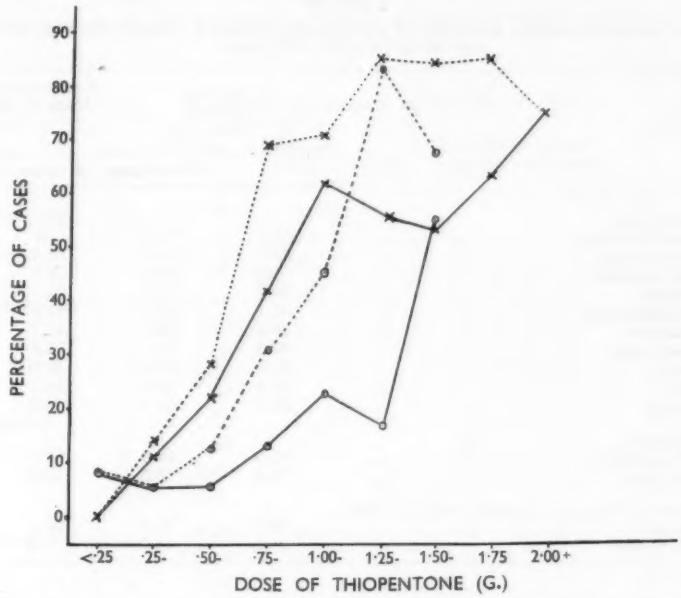

FIG. 2

Correlation between the incidence of hepatic dysfunction and dose of thiopentone administered.

O patients undergoing dilatation and uterine curettage.
X abdominal operations.
... possible liver impairment (urobilinogen excretion ±).
— definite liver impairment (urobilinogen excretion +).

undergoing thyroidectomy and menisectomy. However, it is significant when the series is analyzed as a whole.

In only one operation group were there sufficient cases to correlate the incidence of increased urinary urobilinogen excretion to the dose of thiopentone. The results in 168 patients undergoing dilatation and uterine curettage are shown in figure 2. To confirm these findings a similar correlation is made in a group comprising all operations in which the peritoneal cavity is opened (88 inguinal hernia repairs, 30 appendicectomies, 18 hysterectomies, and 12 repairs of incisional herniae). In both series there is a relationship between the dosage of thiopentone and the incidence of increased urinary excretion of urobilinogen after operation. As might be expected, the over-all incidence is higher in patients after abdominal operations, but irrespective of the procedure the incidence is high in all patients who received 750 mg. thiopentone.

In table III an attempt is made to correlate the incidence of increased urinary urobilinogen excretion with the nature and type of operations and the use of muscle relaxants. The minimal disturbance of metabolism occurred in the

TABLE III

Incidence of increased urinary excretion of urobilinogen related to nature and type of operation and the use of muscle relaxants.

	All cases		Cases receiving large doses of thiopentone	
	+	±	+	±
	Percentage of cases			
Individual operations				
Dilatation and curettage	15.1	25.2	23.8	52.4
Inguinal hernia repair	40.0	51.1	63.6	81.8
Varicose vein ligation	14.0	42.0	28.0	77.8
Appendicectomy	36.7	53.3	46.7	80.0
Lumbar sympathectomy	42.5	50.5	61.5	77.0
Plastic operations	36.4	50.0	62.7	91.0
Haemorrhoidectomy	50.0	64.1	72.8	100.0
For hydrocele	40.0	40.0	80.0	80.0
Hysterectomy	33.3	38.8	66.7	77.8
Thyroidectomy	37.5	62.5	50.0	100.0
Nature of operation				
Abdominal operations	41.0	54.6	57.1	76.7
Surface operations	28.0	36.0	50.0	84.0
Operations in which muscle relaxants could be used				
Relaxants used	40.1	56.7	60.4	82.2
Relaxants not used	36.4	43.0	70.0	84.6

patients undergoing dilatation of cervix and uterine curettage, while the greatest excretion of pigment followed the operations of haemorrhoidectomy and thyroidectomy. On the whole, operations on the surface of the body are followed by a smaller urinary excretion of urobilinogen than cases where the peritoneal cavity is opened.

There is no relationship between the use of muscle relaxants in anaesthesia and the excretion of urobilinogen in the urine after operation.

The results of examination of the urine for carbonic anhydrase are shown in table IV, and analyzed in table V. There seems to be no relationship between the presence of this enzyme in the urine and urinary excretion of urobilinogen. The deduced occurrence of intravascular haemolysis is likewise unrelated to whether thiopentone was the main anaesthetic agent employed or whether its use was reserved only for induction of anaesthesia. There are not sufficient cases to permit conclusions about the effect of the various operations, but the results suggest that the duration of the operation (irrespective of its nature) may be an important factor in the occurrence of intravascular haemolysis.

DISCUSSION

The above findings show conclusively that the use of large doses of thiopentone results in an impairment of the ability of the liver to deal with the urobilinogen absorbed from the gut. The results give no guide to the severity of the hepatic dysfunction, but only show the incidence of its occurrence. The percentage of patients showing evidence of liver damage is fairly closely related to the dose of thiopentone administered.

At some operations there is more extra-

TABLE IV

Details of 40 cases in whom urine was examined for the presence of carbonic anhydrase on the first three days after operation

Operation	No. of cases	Average dose of thiopentone (6)	Supplementary agents (No. of cases)				Urobilinogen in urine after operation		No. of cases with carbonic anhydrase in urine
			Nitrous oxide	Ether	Trichlorethylene	Muscle relaxants	+	±	
Dilatation and curettage	3	0.95	3				0	0	0
	6	1.10	3				4	6	0
	3	0.45	3	2	1		0	1	0
Repair of inguinal hernia	3	1.35	3			3	1	2	2
	4	0.50	4	4	0	4	0	0	0
	2	1.50	1			1	0	0	0
	1	0.25	1		1	1	1	1	0
Varicose vein ligation	1	1.30	1				1	1	1
	2	1.00	2		1		0	0	1
	3	0.62	3	1	2		1	2	0
	2	0.40	2	2	1		0	0	1
Haemorrhoidectomy	5	1.10	5		2	4	5	5	0
	1	1.00	1			1	0	0	0
	3	0.35	3	3		1	2	3	1
	1	0.45	1		1	1	0	0	0

TABLE V

Analysis of the results of the estimation of carbonic anhydrase in urine. Findings are related to:
(a) *presence of urobilinogen in urine;* (c) *nature of operation;*
(b) *dose of thiopentone used;* (d) *duration of operation.*

		No. of cases	No. showing carbonic anhydrase in urine	Percentage of cases showing evidence of intramuscular haemolysis
Urobilinogen in urine	+	15	3	20
	±	21	4	19
	0	19	3	16
Anaesthetic agents				
Thiopentone as main		20	4	20
Thiopentone for induction		20	3	15
Operation				
Dilatation and curettage		12	0	0
Repair of hernia		10	3	30
Varicose vein ligation		8	3	37
Haemorrhoidectomy		10	1	10
Duration of operation				
Less than 30 minutes		21	0	0
½–1 hour		14	3	21
1–1½ hours		4	3	75
Longer than 1½ hours		1	1	100

vasation of blood than at others, and following these the liver has to excrete a larger amount of the breakdown products of bilirubin. This is reflected in the findings of table III, where the percentage of abdominal cases showing an excessive urinary excretion of urobilinogen was greater than for surface operations. Following dilatation of the cervix and uterine curettage, where there is very little extravasation of blood, there was the lowest incidence of excessive urinary output of urobilinogen, irrespective of the anaesthetic agent used.

Many factors, other than the anaesthetic agent, may adversely affect the liver function during operation. As regards the nature of the operation, upper abdominal section has the most deleterious effects (Morrison, 1943; Engstrand and Friberg 1945; Tagnon, Robbins and Nicholas, 1948; Zamcheck, Chalmers, and Davidson, 1949). The longer the duration of the operation, the more likely is liver damage to occur (Coleman, 1938). Chronic sepsis, pulmonary tuberculosis (Coleman, 1938), thyrotoxicosis (Boyce and McFetridge, 1938b), intestinal obstruction (Cole and Elam, 1932), advanced carcinoma and severe burns (Hugill, 1950), all cause impairment of liver function. Complications during convalescence likewise increase the risk of hepatic damage.

Among the factors associated with anaesthesia, hypoxia has the most profound effect on the liver (Rich and Resnick, 1926). Falls in blood pressure during operation adversely affect the liver by producing anoxia (Schmidt, Unruh and Chesky, 1942). The early stages of shock may not be manifested by a fall in blood pressure at a time when hypoxia of internal organs, such as the liver and kidneys, has already taken place (Richards, 1944).

These considerations reveal that there are many factors outside the control of the anaesthetist which may have harmful effects on the liver. By avoidance of hypoxia, correction of falls in blood pressure, and the use of minimal doses of non-toxic drugs, he can do much to reduce the effects of the anaesthetic on the liver. The latter has been made possible by the introduction of muscle relaxants. The use of these is frequently combined with intermittent doses of thiopentone and nitrous oxide. With this technique it is unusual to require doses of thiopentone in the order of those shown in table I in the patients in whom it was the main narcotic agent. When the dose of thiopentone exceeds 750 mg., it has been shown in figure 2 that the incidence of hepatic dysfunction following its use is high. Likewise the same figure shows that its use as an induction agent only followed by minimal doses of ether, trichlorethylene, cyclopropane or pethidine appreciably diminishes the risk of liver damage.

This may not be of great importance in routine elective operations where post-operative complications are not likely to occur. One rarely, if ever, hears of a post-operative death being attributed to liver failure. Be this as it may, the results of this investigation show that the use of large doses of thiopentone is an extra hazard for the patient. Minimal doses should always be employed in known cases of hepatic dysfunction or in patients suffering from such diseases as thyrotoxicosis, acute intestinal obstruction, pulmonary tuberculosis, or where a fall in blood pressure during operation is expected.

SUMMARY

The literature on the effects of thiopentone on liver function is reviewed. There is no general agreement as to the hepatotoxic properties of this drug.

The metabolism of urobilinogen and factors affecting it are discussed. The significance of an increased output of urobilinogen as an indication of hepatic dysfunction is reviewed.

Urinary excretion of urobilinogen was measured for three days after operation in 464 patients. The patients are divided into two equally balanced series, each of 232 cases. In one series thiopentone was used as the main narcotic and in the other its use was reserved for induction of anaesthesia. Evidence of intravascular haemolysis was looked for in 40 cases drawn from both series of cases.

The results obtained were analyzed in relation to the dose of thiopentone, nature and type of operation, and the use of muscle relaxants.

Liver dysfunction occurs in an appreciable number of patients when doses of thiopentone exceeding 750 mg. are administered. The incidence of hepatic damage is related to the dose of barbiturate given. It is considered unwise to use large doses of thiopentone in patients who show any evidence of liver damage, or for operations where any factors which may cause it are liable to occur.

ACKNOWLEDGMENTS

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REFERENCES

Boyce, F. F., and McFetridge, E. M. (1938a). *Sth. med. J. Bgham, Ala*, **35**, 31.

—— —— (1938b). *Arch. Surg., Lond.*, **37**, 427.

Brodie, B. B., Mark, L. C., Papper, E. M., Lief, P. A., Bernstein, E., and Rovenstine, E. A. (1950). *J. Pharmacol.*, **98**, 85.

Brodie, B. B., Bernstein, E., and Mark L. C. (1953). *J. Pharmacol.*, **105**, 421.

Carraway, B. M. (1939). *Curr. Res. Anesth.*, **18**, 259.

Cole, W. H., and Elam, R. (1932). *Proc. Soc. exp. Biol., N. Y.*, **29**, 1274.

Coleman, F. P. (1938). *Surgery*, **3**, 87.

Dundee, J. W. (1952). *Brit. J. Anaesth.*, **24**, 81.

Elton, N. W. (1931). *Surg. Gynec. Obstet.*, **53**, 657.

—— (1950). *Amer. J. clin. Path.*, **20**, 901.

Engstrand, L., and Friberg, O. (1944). *Acta chir. scand.*, **92**, supp. 104.

Fairley, H. (1941). *Quart. J. Med.*, **10**, 95, 115.

Fairlie, C. W., Barso, T. P., French, A. B., Jones, C. M., and Beecher, H. K. (1951). *New Engl. J. Med.*, **244**, 615.

Glynn, L. E. (1949). *Ann. R. Coll. Surg. Engl.*, **4**, 382.

Gould, T. C., and Shideman, F. E. (1952). *J. Pharmacol.*, **104**, 427.

Harrison, C. A. (1947). *Chemical Methods in Clinical Medicine*, 3rd Ed., London: Churchill.

Hugill, J. T. (1950). *Anesthesiology*, **11**, 567.

Meyers, F. H., and Peoples, D. (1954). *Anesthesiology*, **15**, 146.

Mordvinova, N. P. (1948). *Khirurgiya*, **1**, 32.

Morrison, L. M. (1943). *Rev. Gastroent.*, **10**, 171.

Pohle, F. J. (1948). *Wis. med. J.*, **47**, 476.

Popper, H., Steigmann, F., and Szanto, P. B. (1949). *Amer. J. Clin. Path.*, **19**, 710.

Rich, A. R., and Resnick, W. H. (1926). *Bull. Johns Hopk. Hosp.*, **38**, 75.

Richards, D. W. (1944). *Bull. N. Y. Acad., Med.*, **20**, 363.

Richards, R. K., and Appel, M. (1941). *Curr. Res. Anesth.*, **20**, 64.

Robinson, J. R. (1950). *J. clin. Path.*, **3**, 142.

Schmidt, C. R., Unruh, R. T., and Chesky, V. E. (1942). *Amer. J. Surg.*, **57**, 431.

Shideman, F. E., Kelly, A. R., Lee, L. E., Lovell, V. F., and Adams, B. J. (1949). *Anesthesiology*, **10**, 421.

—— Gould, T. C., Winters, W. D., Peterson, R. C., and Wilner, W. K. (1953). *J. Pharmacol.*, **107**, 368.

Tagnon, H. J., Robbins, E. R., and Nicholas, M. P. (1948). *New. Engl. J. Med.*, **238**, 566.

Vaizey, J. M. (1938). *Brit. J. Anaesth.*, **15**, 55.

Walker, J. M., and Wynn Parry, C. B. (1949). *Brit. J. Pharmacol.*, **4**, 93.

Walton, C. H., Uhl, J. W., Egner, W. M., and Livingstone, H. M. (1950). *Arch. Surg., Chicago*, **60**, 986.

—— Saldamando, J., and Egner, W. M. (1951). *Anesthesiology*, **12**, 67.

Zamcheck, N., Chalmers, T. C., and Davidson, C. S. (1949). *Amer. J. Med.*, **7**, 409.

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PROLONGED APNOEA AFTER SUXAMETHONIUM IN MAN

BY

D. E. ARGENT, O. P DINNICK, AND F. HOBBIGER

Middlesex Hospital, London

SUXAMETHONIUM produces in man muscular relaxation of shorter duration than that produced by equipotent doses of tubocurarine or decamethonium and for this reason it is nowadays often used in preference to other muscular relaxants in cases where only a short action is required.

It has been stated that in the same person a fixed dose of suxamethonium, given at suitable intervals, produces a constant response, and in a given individual the duration of paralysis increases with increasing doses (Thesleff, 1952).

With single injections neuromuscular block of the desired intensity can be produced only in doses which also arrest respiration. If 1 mg./kg. is given intravenously, respiration is arrested within 1 minute of the injection and the apnoea lasts for a period of 3–5 minutes. During the last three years numerous cases have been reported in which the arrest of respiration lasted for much longer periods of time, and in some cases it was hours before adequate normal respiration returned. This prolonged effect of suxamethonium has been attributed to a low plasma cholinesterase level for the following reasons:

(1) Plasma-cholinesterase (in the literature often referred to as pseudo-cholinesterase as distinct from the true cholinesterase which is present in red cells) catalyses the hydrolysis of suxamethonium (succinyldicholine). This hydrolysis affects in the first stage only one ester link and yields succinylmonocholine and choline; the hydrolysis of the second ester link is a much slower process than the hydrolysis of the first and yields succinic acid and choline. Succinylmonocholine has only 1/10–1/50 of the activity of the dicholine, and succinic acid and choline can be considered as pharmacologically inert in the concentrations which arise at any given moment (Glick, 1941; Bovet, Bovet-Nitti, Guarino, Longo and Fusco, 1951; Whittaker and Wijesundera, 1952; Lehmann and Silk, 1953: Foldes, 1953).

(2) In man the duration of apnoea induced by suxamethonium is inversely related to the level of plasma cholinesterase (Evans, Grey, Lehmann and Silk, 1953).

During the past two years we have had seven cases of prolonged apnoea in patients who have received suxamethonium* while undergoing an operation.

CASE REPORTS

Case 1.

A man, aged 27, weighing 67 kg., was operated upon for the excision of a small perineal sinus. One hour pre-operatively he received 1/50 gr. (1.3 mg.) atropine

* In all cases suxamethonium chloride (Allen and Hanburys) was used, and throughout the text dosages refer to the salt.

by mouth. Induction of anaesthesia was commenced with 400 mg. thiopentone sodium and continued with 80 per cent nitrous oxide and 20 per cent oxygen. Five minutes later 75 mg. of suxamethonium were given slowly i.v. and the resulting apnoea persisted for 50 minutes. At this time diaphragmatic breathing returned but was inadequate to maintain oxygenation and respiration was assisted for a further 60 minutes before recovery was complete.

Case II.

A man, aged 39, weighing 45 kg., received 100 mg. pethidine and 1/150 gr. (0.45 mg.) scopolamine one hour before induction of anaesthesia for aortography to identify a large retroperitoneal tumour. Anaesthesia was induced with 500 mg. thiopentone sodium and continued with 80 per cent nitrous oxide and 20 per cent oxygen, to which a small quantity of trichlorethylene was added. 30 mg. of suxamethonium were injected i.v. while the first series of films were taken. Recovery from the apnoea after this dose of suxamethonium took 5 minutes. A further 30 mg. of suxamethonium were injected 15 minutes later for a second series of films, and apnoea in this instance persisted for 10 minutes. As still more films were required another 30 mg. suxamethonium were injected 20 minutes after recovery from the second dose was complete. This third injection was followed by an apnoea lasting for 30 minutes. Diaphragmatic respiration returned then but was grossly inadequate for the maintenance of full oxygenation and respiration had to be assisted for a further 3 hours. 5 ml. of nikethamide were given during this period and produced a temporary improvement. 1 pint of fresh blood was given with no improvement, but after 1 mg. of neostigmine normal respiration was eventually restored.

Case III.

A fit man, aged 72, weighing 80 kg., was operated upon for the excision of a malignant melanoma. One hour pre-operatively he received 100 mg. pethidine and 1/150 gr. (0.45 mg.) scopolamine. Induction of anaesthesia was with 400 mg. thiopentone sodium and 40 mg. suxamethonium were given a few minutes later for the purpose of intubation. Normal respiratory rhythm failed to return for 50 minutes.

Case IV.

A woman, aged 54, weighing 82 kg., was anaesthetized for the repair of a ventral hernia. Anaesthesia was induced with 700 mg. thiopentone sodium and maintained with a mixture of 80 per cent nitrous oxide and 20 per cent oxygen to which a small quantity of trichlorethylene was added. 60 mg. of gallamine triethiodide were given to promote relaxation. 45 minutes after the injection of gallamine at a time when muscular tone had returned to its normal level, 50 mg. of suxamethonium were given. This dosage of suxamethonium produced an apnoea which showed no sign of abatement after 35 minutes, when 1.25 mg. of neostigmine were injected. Neostigmine produced no improvement and it took six hours (from the onset of apnoea) before normal respiratory rhythm was restored.

Case V.

A man, aged 55, weighing 67 kg., was anaesthetized for toilet and skin grafting to severe burns. The patient received 400 mg. thiopentone sodium 10 minutes after the administration of 1/150 gr. (0.45 mg.) scopolamine and 1/3 gr. (20 mg.) papaveretum. Anaesthesia was maintained with cyclopropane and oxygen for 5 minutes and to facilitate intubation 50 mg. of suxamethonium were then given. The injection of the latter was followed by an apnoea which persisted for 75 minutes.

Case VI.

A man, aged 56, weighing 70 kg., was anaesthetized for the evaluation of a carcinoma of the tongue and subsequent insertion of radium needles. One hour pre-operatively he was given 1/6 gr. (10 mg.) morphine and 1/100 gr. (0.65 mg.) atropine. Anaesthesia was induced with 300 mg. thiopentone sodium and continued with 80 per cent nitrous oxide and 20 per cent oxygen, to which a small amount of ether was added. In order to facilitate intubation 30 mg. of suxamethonium were given. After the apnoea, which followed this injection, had lasted for 60 minutes, 1.25 mg. of neostigmine were given and produced some improvement in the respiratory attempt. Complete recovery occurred 30 minutes later.

Case VII.

A woman, aged 50, weighing 68 kg. was given 1/3 gr. (20 mg.) papaveretum and 1/150 gr. (0.45 mg.) scopolamine 70 minutes prior to induction of anaesthesia for dilatation and curettage. 450 mg. thiopentone sodium were then given i.v. and acute laryngeal spasm ensued. Attempts were made to obtain an airway, but this was found to be impossible due to masseteric spasm. Cyanosis became marked and 50 mg. suxamethonium were given some 2 minutes after the onset of spasm. Relaxation was obtained and oxygen under pressure rapidly restored the patient's condition. Complete apnoea, however, persisted for 21 minutes when some diaphragmatic respiration returned. Ten minutes later 2.5 mg. neostigmine were given since respiration was still inadequate; this rapidly restored normal respiration.

All the seven patients have been examined following the incidents and no evidence or history of liver disease could be found. None of the patients had been in contact with insecticides or related chemical compounds and none felt any the worse for the prolonged apnoea. Complete amnesia was present in all cases extending not only over the period of absolute apnoea but also for the period during which the respiration was present but inadequate to maintain satisfactory oxygenation. In every case this period of

inadequate respiration lasted for a considerable time; diaphragmatic movements returned first and a tracheal tug was present but elsewhere a complete flaccid paralysis existed. The corneal reflex was next observed to return, and once this reflex had returned consciousness and complete recovery occurred within a short time. During the period of paralysis neostigmine was given to cases II, IV, VI, and VII. In case IV no improvement was seen. In case VI respiration deepened but recovery was not complete and in cases II and VII complete recovery followed the injection of neostigmine.

Richards and Youngman (1952) and Durrans (1952) have suggested that prolonged apnoea after suxamethonium might be due to some combined effect of respiratory depressant drugs and hyperventilation. This is almost certainly the explanation for several cases which we have seen where apnoea persisted up to 20 minutes, but the patients do not show the characteristic prolonged stage of partial recovery of respiration following a shorter period of complete apnoea as seen in the cases just described.

We have attempted to avoid acapnia in our cases by adding from time to time small amounts of CO_2 to the oxygen with which artificial respiration was necessarily maintained during apnoea but we have seen no beneficial effect from it. The alternative possibility of there being an excessive "build-up" of CO_2 was also kept in mind. We are, however, confident that this did not occur except perhaps in case IV who was a short, fat and bronchitic patient.

We have measured the plasma-cholinesterase level in these patients on the day following the operation, and from the data we have obtained, we conclude that in our patients a reduction in plasma-cholinesterase level cannot be the main cause, but only a contributory factor for the prolonged apnoea.

TECHNIQUE USED FOR THE DETERMINATION OF PLASMA CHOLINESTERASE LEVEL

Determinations of cholinesterase activity were carried out by the manometric technique at 37°C in an atmosphere of 95 per cent N_2 and 5 per cent CO_2. In each test the total volume of fluid was kept constant at 3 ml. and made up by 0.2 ml. plasma, 0.025 molar $NaHCO_3$ and benzoylcholine chloride (final concentration: 0.01 molar). Under such conditions the hydrolysis of benzoylcholine (which is a specific substrate for the enzyme under investigation) by plasma-cholinesterase (present in plasma) yields acid which in turn liberates CO_2 from the $NaHCO_3$. The amount of CO_2 liberated in a given time is measured and gives the enzyme activity. For our work we have chosen the µl. of CO_2 which were liberated from the $NaHCO_3$ solution during a period of 30 minutes (covering the time from 5 to 35 minutes after addition of substrate) as the index of cholinesterase activity.

It is well known that the plasma-cholinesterase level varies considerably from person to person, and Callaway, Davies and Rutland (1951) who measured it in 247 healthy human beings in England found a coefficient of variation of the enzyme level of 21.7 per cent with the fiducial limits of variation covering a range of 57 to 142 per cent of the mean. It was not possible to ascertain the plasma-

Plasma-cholinesterase level in the patients with prolonged apnoea.

Case No.	Sex	Age	Weight in kg.	Dose of suxamethonium	Total duration of apnoea in min.	Plasma-cholinesterase in μl/CO_2/30 min./ml. plasma
I	male	27	67	75	110	582
II	male	39	45	30, 30, 30	5, 10, 210	718
III	male	72	80	40	50	340
IV	female	54	82	50	360	30
V	male	55	67	50	75	830
VI	male	56	70	30	90	584
VII	female	50	68	50	31	525

cholinesterase levels of the relatives of Case IV, the only case with a significantly low plasma-cholinesterase level (Forbat, Lehmann and Silk, 1953).

Because of the small number of cases we thought it would be best to compare the plasma-cholinesterase level in patients with a prolonged apnoea with the plasma-cholinesterase level in patients who had given a "normal" response to suxamethonium. We selected for this purpose seven patients who were in age, sex and weight similar to those with prolonged apnoea. Their plasma-cholinesterase level was found to be 838 ± 244 (i.e. mean ± S.D.), compared with 516 ± 263 in the the patients with prolonged apnoea. In six instances the patient with prolonged apnoea was found to have a plasma-cholinesterase level above 50 per cent of that of the control case (case IV being the exception) and in cases II and VI the plasma-cholinesterase level differed by less than 10 per cent from the controls.

DISCUSSION

Suxamethonium is a synthetic, quaternary ammonium base, which competes with acetylcholine for certain structural elements of the motor endplate, which are generally referred to as "receptors"; the combination of suxamethonium with these receptors leads to a depolarization of the motor endplate which is the cause of the neuromuscular block. The duration of action of suxamethonium depends on the stability of the suxamethonium-receptor complex and the concentration of free suxamethonium at the motor endplate region. In patients with a "normal" response the receptor-suxamethonium complex is very unstable, and the dose given, the rate of metabolism, excretion and redistribution of the drug are factors which determine the duration of neuromuscular block. A prolonged action of suxamethonium may be caused by an aberration either of one or more of these processes.

The rate at which suxamethonium is hydrolysed by plasma-cholinesterase depends on the enzyme concentration. Thesleff (1952) found in cats that the duration of paralysis is doubled when the dose is increased by 4 times or more. Bourne (1953) gives similar figures for patients with a "normal" response to suxamethonium. The injection of 1.5 mg. neostigmine (a dose which produces marked inhibition of plasma-cholinesterase activity) in a patient of 50 kg. only doubles the duration of action of suxamethonium (Thesleff, 1952). If plasma-cholinesterase were the only factor deter-

mining the duration of action of suxamethonium a reduction of the enzyme level to 25 per cent would be required in order to double the duration of paralysis. With one exception the plasma-cholinesterase in the patients with prolonged apnoea was never below 50 per cent of that of patients with a "normal" response and apnoea should, therefore, not have persisted for longer than 10 minutes at the utmost. Evans *et al.* (1953), Wolfers (1952) and Swerdlow (1954) also describe cases in which prolonged apnoea was seen in spite of a normal plasma-cholinesterase level. There is thus good reason to assume that the prolonged apnoea is not always a reflection of a reduced plasma-cholinesterase level and that other factors must be involved.

It is now well established that in a number of cases the duration of action of a drug is determined by redistribution of the drug rather than by its destruction and excretion. This is exemplified by the well-known transference of general anaesthetic agents from the blood stream to the tissues. The same process, however, must also take place on a smaller scale; a local redistribution takes place when small doses of a drug move from its point of action to the surrounding tissues. For example, the transient nature of neuromuscular block produced by tubocurarine is fully explained on such a basis (Marsh, 1952).

We experimented with cats under chloralose anaesthesia and recorded the changes in tension of the tibialis anterior muscle during intermittent stimulation of its nerve by supramaximal electrical stimuli. We found that the recovery of neuromuscular transmission from block after a single small injection of decamethonium or suxamethonium was identical regardless of whether the blood supply to the muscle was undisturbed or the muscle rendered completely ischaemic at the peak of paralysis. These findings can only be interpreted in terms of a local redistribution of decamethonium and suxamethonium, i.e. in the case of single small injections the blocking agents are first preferentially accumulated at the motor endplate region but later an equilibrial state is established between the endplate region and the adjacent areas; recovery of neuromuscular transmission is thus guaranteed and must not necessarily involve removal of the blocking agent *via* the blood stream or by enzymatic destruction.

This theory of redistribution is not incompatible with the observations of Bourne (1953) and Evans *et al.* (1953), as it would now appear that the plasma-cholinesterase determines the amount of suxamethonium which reaches the endplate and a reduction in enzyme level will, therefore, reflect itself in minor prolongations of the duration of paralysis.

Churchill-Davidson and Richardson (1953) found that neuromuscular block induced by decamethonium in the clinically weak muscles of myasthenic patients has the characteristics of a block induced by tubocurarine and is reversible by neostigmine, whereas in "normal" patients it depolarizes the endplate and this block is not reversed by neostigmine. Suxamethonium has the same mode of action as decamethonium and we must, therefore, consider the possibility that in certain patients the receptor-suxamethonium complex behaves in the same way as described by Churchill-Davidson and Richardson for

decamethonium. This could explain the beneficial effects of neostigmine which were seen in some of our patients suffering from prolonged apnoea.

There is also evidence that decamethonium has an action on the muscle fibre outside the endplate region (Jarcho, Berman, Eyzaguirre and Lilienthal, 1951) and we have no reason to assume that this does not also hold for suxamethonium. In addition we must consider that functional recovery of neuromuscular transmission depends upon certain metabolic processes which restore the muscle fibre itself to its original state of organization after depolarization.

In normal human volunteers an intravenous injection of a dose of suxamethonium sufficient to cause complete neuromuscular block does not affect consciousness or sensations (Mayrhofer, 1952). On the other hand, Ellis, Morgan and de Beer (1952) found that tubocurarine, decamethonium and suxamethonium when given intravenously in cats had a depressant action on the respiratory centre when used in high concentrations. This might well also be the case under exceptional conditions in man and the beneficial effects of niketharnide described by Richards and Youngman (1952) seem to support this idea. Such a central action of suxamethonium would usually be masked by the depression produced by anaesthetic agents but could nevertheless explain some cases of prolonged apnoea. The absence of a corneal reflex and dilated pupils which was observed in cases I and II in the absence of clinical anoxia or strong afferent stimulation, offers support to this theory.

In the light of our present knowledge it is impossible to say in any individual case whether failure of local redistribution, altered response of the motor endplate, slow recovery of the muscle fibres or an action on the central nervous system is mainly responsible for a prolonged apnoea following suxamethonium.

The suggestion that in cases such as those reported by us, the lack of enzymatic hydrolysis of suxamethonium is not the main cause for prolonged apnoea is fully supported by reports of Harris and Dripps (1950), Hurley and Monro (1952) and Rizzi and Ricci (1953), who observed prolonged apnoea following an injection of decamethonium, a substance which acts like suxamethonium but is not metabolized enzymatically.

TREATMENT

The incidence of prolonged apnoea, 1 in 1200 cases in our hands, does not appear great enough to outweigh the many advantages of the drug.

The use of a single small test dose does not exclude the possibility of a prolonged apnoea ensuing as increased sensitivity may occur as in Case II.

This is not necessarily true where the response is assayed by the slow injection of a dilute solution preparatory to the use of a continuous infusion technique. We would emphasize that the cases and discussion in this communication concern the single dose technique where it may well be that the temporary high concentration of the drug is responsible for the effects produced.

The detailed management of prolonged apnoea is beyond the scope of this discussion, but in spite of the possibility of a central action we believe it advisable that

ventilation be carried out with a narcotic nitrous oxide and oxygen mixture. The fact that this was not done in all our cases and that no harm resulted does not invalidate this principle, as cases have been reported where consciousness was present during the period of apnoea.

The fact that neostigmine has a direct stimulant effect on muscle fibres and the work of Churchill-Davidson suggested that it was worthy of trial in these cases. However, our experience in Case IV supports that of Harper (1952) in that it should not be given when the paralysis is still complete.

Encouraging results were obtained, however, when neostigmine—preceded by atropine—was given during the stage of partial recovery; when respiration, although established, was accompanied by a tracheal tug and was insufficient to maintain an adequate gaseous exchange.

SUMMARY

The plasma-cholinesterase level in six (out of seven) patients who had a prolonged apnoea after suxamethonium was not reduced to such an extent that the reduced enzyme level could be held solely responsible for the apnoea.

No satisfactory explanation can be given for the prolonged apnoea but certain mechanisms which could be involved are discussed.

The successful use of neostigmine in some cases of prolonged apnoea is described.

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REFERENCES

Bourne, J. G. (1953). *Brit. J. Anaesth.*, **25**, 116.
Bovet, D., Bovet-Nitti, F., Guarino, S., Longo, V. G., and Fusco, R. (1951). *Arch. int. Pharmacodyn.*, **88**, 1.
Callaway, S., Davies, D. R., and Rutland, J. P. (1951). *Brit. med. J.*, **2**, 812.
Churchill-Davidson, H. C., and Richardson, A. T. (1953). *J. Physiol.*, **122**, 252.
Durrans, S. F. (1952). *Lancet*, **2**, 145.
Ellis, C. H., Morgan, W. V., and de Beer, E. J. (1952). *J. Pharmacol.*, **106**, 353.
Evans, F. T., Grey, P. W. S., Lehmann, H., and Silk, E. (1953). *Brit. med. J.*, **1**, 136.
Foldes, F. F., (1953). *Proc. Soc. exp. Biol., N.Y.*, **83**, 187.
Forbat, A., Lehmann, H., and Silk, E. (1953). *Lancet*, **2**, 1067.
Glick, D. (1941). *J. biol. Chem.*, **137**, 357.
Harper, J. K. (1952). *Brit. med. J.*, **1**, 866.
Harris, L. C. jr., and Dripps, R. D. (1950). *Anesthesiology*, **11**, 215.
Hurley, M. J., and Monro, A. B. (1952). *Brit. med. J.*, **1**, 1027.
Jarcho, L. W., Berman, B., Eyzaguirre, C., and Lilienthal, J. L. jr. (1951). *Ann. N.Y. Acad. Sci.*, **54**, 337.
Lehmann, H. and Silk, E. (1953). *Brit. med. J.*, **1**, 767.
Marsh, D. F. (1952). *J. Pharmacol.*, **105**, 299.
Mayrhofer, O. K. (1952). *Brit. med. J.*, **1**, 1332.
Richards, H., and Youngman, H. R. (1952). *Brit. med. J.*, **1**, 1334.
Rizzi, R., and Ricci, C. (1953). *Curr. Res. Anesth.*, **32**, 400.
Rudell, J. S. (1952). *Lancet*, **2**, 341.
Swerdlow, M. (1954). *Curr. Res. Anesth.*, **33**, 201.
Thesleff, S. (1952). *Acta physiol. scand.*, **25**, 348.
Whittaker, V. P., and Wijesundera, S. (1952). *Biochem. J.*, **52**, 475.
Wolfers, P. (1952). *Brit. med J.*, **2**, 778.

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THE USE OF NORADRENALINE IN ACUTE HYPOTENSION IN SURGICAL CASES

BY

E. F. SHANAHAN

Liverpool Royal Infirmary

INTRODUCTION

THIS article was prompted by an unusual run of severely shocked surgical emergencies in a very short time and it records the treatment of 19 cases of circulatory collapse over a period of fifteen months and it points to the efficacy of l-noradrenaline administered intravenously before, during, and after operation.

TECHNIQUE

Noradrenaline may be administered by adding the contents of one 2-ml. ampoule of the solution (Levophed) to a 1-pint (450-ml.) bottle of isotonic sodium chloride solution, 5 per cent dextrose solution, Dextran, plasma or blood. Each millilitre of solution now contains approximately 4 μg. of noradrenaline. The solution is given intravenously through a drip transfusion apparatus which allows accurate estimation of the rate of flow in drops per minute. Blood pressure readings are taken regularly throughout the period of administration; at first, readings taken every thirty seconds are necessary, as there is a danger of overdosage. But as the patient becomes stabilized the interval can safely be increased to five, ten, or even fifteen minutes.

The rate of flow is determined solely by the response of the patient's systolic blood pressure. Sufficient is given to restore it to the patient's usual level (if previously known) or 130 mm. Hg if not. Once this level is reached it is maintained by adjusting the rate of the drip. Sudden stopping of the drip is found to lead to an alarming fall in blood pressure. It is very important therefore to keep a careful watch on the infusion and set up another, if it shows signs of failing.

RESULTS

It will be seen from tables I, II, and III that there was a response to administration of the drug in all except three patients. Of those patients which failed to respond, two were subsequently found to be cases of cardiac failure and the third a case of profuse vena-caval haemorrhage. The degree of response was variable. Some cases improved dramatically with immediate elevation of the blood pressure to normal or above-normal levels, whereas others showed only a slight or moderate result. It was noted that the degree of response to the drug was significantly related to the cause of the collapse. This will be discussed later.

Of the nineteen cases treated, seven died. This is a high proportion, but it must be remembered that all of these cases were desperately ill when treatment com-

[continued on page 34

TABLE I

Cases treated before operation

Case No.	Initials	age	Cause of collapse	Systolic blood pressure: Before treatment	Systolic blood pressure: During treatment	Response	Drip rate per minute: Initial	Drip rate per minute: Maintenance	Duration of treatment (hours)	
1	A.S.	45	Haemorrhage; ruptured spleen	N.P.	80 120 with blood	+	60	30—35	4	Recovery after splenectomy.
2	O.T.	57	Large duodenal perforation	N.P.	120	++	45	30—35	10	Recovery after suture of perforation.
3	J.McG.	64	Large duodenal perforation	N.P.	140	++	45—50	35	24	Recovery after suture. Died of subsequent reperforation (10 days post-operation).
4	I.C.	56	Large bowel obstruction; very marked dehydration	60	100	+	45	30—40	26	Withstood transverse colostomy. Survived resection of pelvic colon later.

TABLE II

Cases treated during operation

5	L.S.	50	Abdomino-perineal resection of rectum (synchronous)	N.P.	120	++	50	30	96	Survived.
6	J.E.	54	Abdomino-perineal resection of rectum (synchronous)	N.P.	130	++	45	30—40	20	Survived.
7	M.L.	60	Massive vena-caval haemorrhage during nephrectomy	N.P.	N.P. (Pulse returned) 120 with blood	+?	60	30—40 (with blood)	6	Survived.
8	J.W.	55	Cysto-prostatectomy and transplantation of ureters	70	120	+	45	30—40	18	Immediate survival. Died 3 weeks later from lung suppuration.
9	P.F.	63	Cysto-prostatectomy and transplantation of ureters	N.P.	N.P.	—	60	—	20 mins.	No response. Died on table. Post-mortem—cardiac failure.
10	F.McW.	78	Acute large bowel obstruction very poor myocardium	N.P.	120	+	60	40	72	Died during treatment. Post-mortem—cardiac failure.
11	M.L.	69	Acute large bowel obstruction very poor myocardium	N.P.	N.P.	—	60	—	3	Died 2½ hours after colostomy. Post-mortem — cardiac failure.
12	J.T.	64	Prostatectomy; fall of systolic blood pressure	80	120	+	45	30—40	6	Survived.
13	P.McL.	67	Prostatectomy; fall of systolic blood pressure	N.P.	110	+	45	30—35	100	Survived.

N.P.=not perceptible.

N.P.=not perceptible.

TABLE III

Cases treated after operation

Case No.	Initials	age	Cause of collapse	Systolic blood pressure: Before treatment	Systolic blood pressure: During treatment	Response	Drip rate per minute: Initial	Drip rate per minute: Maintenance	Duration of treatment (hours)	
14	E.M.	67	Pancreatico-duodenectomy; delayed post-operative collapse	N.P.	120	++	45	30—40	44	Recovered from collapse. Survived.
15	A.W.	54	Restoration of common bile duct; delayed post-operative collapse	N.P.	110	++	45	35	43	Recovered from collapse. Survived.
16	E.J.	62	Cholecystectomy; post operative peritonitis	N.P.	130	++	45	30—35	60	Recovered from collapse when infection was localized. Subphrenic abscess subsequently drained. Died later from pericardial suppuration.
17	M.C.	70	Coronary thrombosis 14 days after resection of rectum	N.P.	120	++	45	35	30	Recovered from collapse. Died at home from second coronary.
18	B.S.	87	Profuse haemorrhage following prostatectomy	80	110	+	45	30	7	Died suddenly during administration. Post-mortem—massive pulmonary oedema.
19	J.H.	57	Small bowel strangulation after resection of rectum; collapse during second operation; noradrenaline commenced after second operation	—	80–120	+	60	45 rising to 80	12	Died of peritonitis.

N.P.=not perceptible

menced. Furthermore, as table IV shows, the cause of death in six cases was the continuing effect of the lesion which originally caused the collapse or the onset of a further complication. The seventh case (Case No. 18), however, died suddenly during administration of noradrenaline. Post-mortem revealed massive pulmonary oedema. Experimentally the commonest result of administration of toxic doses of noradrenaline is the production of pulmonary oedema (MacKay and Pecka, 1950) and it is therefore possible that the patient's death in this instance may have been accelerated.

DISCUSSION

In 1934, Bacq put forward the theory that noradrenaline might be the transmitter substance at sympathetic nerve endings. Euler, in 1946, demonstrated that extracts of organs contained a substance indistinguishable from noradrenaline. Goldenberg, Pines, Baldwin, Greene, and Roh (1948) showed that noradrenaline caused vasoconstriction of peripheral vessels whereas it did not influence the cardiac output. In 1949, Goldenberg, Apgar, Deterling, and Pines first published the therapeutic effects of this drug. They used it, with effect, in the treatment of hypotension following thoraco-lumbar sympathectomy. In 1951, Swan, and also Cahill and Monteith, described cases in which it was administered following removal of phaeochromocytomata.

In 1952, Swan reviewed the literature and pharmacology of the drug when it was again stressed that its action was essentially vasoconstricting without any appreciable effect on the cardiac output or heart rate, that it acted as a dilator of the coronary vessels, and he postulated that it might be useful as a therapeutic agent for various types of acute hypotension.

Livesey and Chapman (1953) presented a series of cases in which it was used for acute hypotension in medical conditions, and about the same time Crawford and Haynes (1953), Bergmann (1952), and Barlow, Ginsberg and Sottleck (1953) described its use in a series of cases with surgical circulatory collapse.

In 1952 Wells and Gray, and again in 1953 Wells, described the use of noradrenaline in the avoidance of anuria resulting from hypotension following extensive and traumatic operations such as excision of the head of the pancreas and total cystectomy.

This series represents a further study in the use of noradrenaline in conditions of acute hypotension in surgical cases.

In table V a comparison is drawn between the probable physiological lesion underlying the acute hypotension and the response to treatment. The results tally, more or less, with the known pharmacological effects of the drug.

The cases which responded best to administration of noradrenaline were (as might be expected) those of pure peripheral vascular failure uncomplicated by blood loss. These all showed an immediate and dramatic rise of systolic blood pressure. Perhaps the most satisfying results in this group were the cases of pre-operative shock subsequently treated successfully by operation and the two cases of "idiopathic" post-operative shock. In this latter type of case there was no new complication causing this collapse, but it would appear that it was a delayed reaction to a severe operation. This type

TABLE IV

Analysis of cause of death after response to treatment

Case No.	Cause of collapse	Response to noradrenaline	Results
		(*a*) DIED DURING ADMINISTRATION	
18	Severe haemorrhage following prostatectomy	Good initially	Sudden collapse after 7 hours treatment. Post-mortem examination—massive pulmonary oedema.
19	Internal strangulation following resection of rectum	Good initially	8 hours treatment. Died of peritonitis.
10	Paul Mickulicz resection of sigmoid for carcinoma with obstruction	Good initially	Died after 72 hours treatment. Post-mortem examination indicated cardiac failure.
		(*b*) RECOVERED FROM HYPOTENSION BUT DIED SUBSEQUENTLY	
3	Large duodenal perforation	Very good	Subsequent suture of perforation successful. Died 10 days later from reperforation.
8	Total cystectomy, etc.	Good	Died 6 weeks later from lung abscess.
16	Upper abdominal peritonitis cholecystectomy	Very good	Subphrenic abscess drained 1 week later. Died 3 weeks later from spread of infection to pericardium.
17	Coronary thrombosis	Good	Recovered. Died from second attack after discharge.

TABLE V

Relation between lesion and response

Cause of hypotension	No. of cases	Response to noradrenaline	Results
(1) Peripheral circulatory failure only			
(*a*) Serious organic lesion	4	Excellent in 3	3 recovered from hypotension but 2 died later from recurrence or spread of the original lesion.
(*b*) " Idiopathic " post-operative collapse	2	Excellent	Both recovered.
(2) Haemorrhage plus peripheral circulatory failure	6	Very good	5 survived; 1 died from lung abscess 6 weeks later.
(3) Haemorrhage only	3	Varied; slight to moderate	2 recovered; 1 died suddenly during treatment from massive pulmonary oedema.
(4) Cardiac failure only	2	None	Both died almost immediately.
(5) Cardiac failure plus peripheral circulatory failure	2	Good initial response	Both cases died later from cardiac condition.

of delayed post-operative shock is not unknown and heretofore has been the cause of many deaths in otherwise successful operative procedures. Both our cases responded dramatically to administration of noradrenaline, and after a period of 43 hours in one and 44 hours in the other the drug could be discontinued. Their subsequent convalescence was uneventful.

There were four cases in which we considered collapse to be due to peripheral circulatory failure only, but which had a definite organic cause (e.g., peritonitis). In these cases also the initial response was dramatic, but their eventual recovery depended on whether or not this organic cause could be eradicated.

The second group consists of those patients in which the cause of hypotension was presumably a mixture of peripheral vascular failure due to surgical and anaesthetic shock plus a diminished blood volume due to blood loss. This type of collapse was found in elderly patients undergoing major and prolonged surgical intervention. It was found that in this type of case the blood pressure sometimes fell alarmingly in the second or third hour during operation and that the fall could not always be counteracted by replacement of blood alone. The response of these patients to noradrenaline was on the whole very good. In most cases the addition of noradrenaline to the blood drip caused a rapid rise of systolic blood pressure to normal or near normal levels, this level being maintained for the duration of the operation. There were six cases of this nature and all except one recovered. Noradrenaline administration had to be continued in the post-operative phase for varying periods.

The third group, three in number, consists of those cases in which the main or perhaps only cause underlying the onset of acute hypotension was profuse haemorrhage.

The response in this type of case was found to be slight to moderate. In severe haemorrhage in an otherwise healthy subject one would expect maximal vasoconstriction and therefore very little, if any, response to vasoconstricting agents. Yet, in one of our cases, a patient with a ruptured spleen (Case No. 1), a blood pressure previously imperceptible was raised to 80 mm. Hg and maintained at that level until blood became available. In the case, previously mentioned, of severe haemorrhage following prostatectomy (Case No. 18) there was also good initial response. In the third case of this group, a case of profuse vena-caval haemorrhage during nephrectomy (Case No. 7), the pulse did return following rapid noradrenaline administration (60 drops per minute) but the systolic blood pressure did not become detectable until blood was administered. It might be argued that noradrenaline by raising the blood pressure might increase haemorrhage in cases of arterial bleeding. There is evidence that this occurred in Case No. 18 (haemorrhage after prostatectomy) but not in Case No. 1. In two patients in which noradrenaline was administered during prostatectomy (Cases No. 11 and 12) the patients' condition improved but the haemorrhage in the prostatic cavity was not appreciably increased thereby. With regard to this type of case it is felt that blood in combination with noradrenaline led to a more rapid resuscitation than blood alone.

This was noted also by Cappe and Pallin (1951) and by Churchill-Davidson (1951). The former, in three obstetric cases of massive bleeding, found no effect on the blood pressure even after transfusion of a large quantity of blood; it was only with noradrenaline that the first response could be obtained. The latter advises it when even large quantities of blood fail to restore the circulation sufficiently to guarantee an adequate supply of blood to vital organs. Livesey and Chapman (1953) also found a pressure response possible in cases with acute haemorrhagic shock, not reversible by blood transfusion alone.

The fourth group consists of two patients in whom noradrenaline was administered for cardiac failure, in the hope that there might be some element of peripheral circulatory failure present. The diagnosis was confirmed at post-mortem examination in each case. There was no response to noradrenaline.

In two cases in which there was a mixture of cardiac and peripheral circulatory failure (Cases No. 17 and 10, both coronary thrombosis) there was a good response to noradrenaline infusion initially but both patients succumbed to their cardiac condition later.

It must be pointed out that prompt restoration of the systolic blood pressure in acute haemorrhagic and traumatic hypotension is a line of treatment which is not universally accepted. There is another school of thought which has come mainly from France in the work of Laborit and Huguenard (1954) but also finding expression in this country in the papers of Wyman (1953) and some others.

Their postulation is that overaction of the sympathetic nervous system in states of shock may be harmful in its effect and that this overaction is best countered by the administration of drugs which paralyse the ganglia of the sympathetic system. By this means they convert a case of uncontrolled hypotension into one of "controlled hypotension" similar to the condition attained in the practice of hypotensive anaesthesia. Their argument is supported by successful experiments on animals (Laborit, 1950) and by clinical trial (Laborit and Huguenard, 1954). Similar experimental work has been done in America by Crumpton, Murphy, Wittimore, Copps, and Orth (1952). Recently these drugs have been used fairly extensively with allegedly good results in the campaign in Indo-China (Nicol, Mattei, Brun-Buisson, Francois, Jaffry, and Lagneau, 1953; Chippeaux, 1954).

This line of treatment is not without its hazards, and its use in this country is, at the moment, confined to large centres where skilled personnel and consulting services are readily available.

The French work was commenced before the isolation of noradrenaline as a pressor agent and before it was generally realized that noradrenaline was the active transmittor substance at sympathetic nerve endings. It may well be that their rather unfavourable attitude towards the efficiency of the sympathetic system in states of shock may be based on the inefficiency of adrenaline as a pressor agent as shown by animal experiments and clinical trial.

One does not deny the value of the French work. It seems, however, in the light of present knowledge, unphysiological. After all, "shock" is due to dispro-

portion between the blood volume and the capacity of the vascular bed. In theory, the ideal treatment of this condition is to restore blood volume and to diminish the capacity of the vascular bed with an efficient vasoconstricting agent. Up to then the effective natural pressor agent had not been discovered, therefore this ideal could not be attained. Heretofore adrenaline was considered to be the natural pressor agent, and as results with it were poor, then the theory underlying the treatment became suspect and alternative ideas were suggested.

Now, however, noradrenaline has been discovered and has given good results in practice. It is, in the writer's opinion, far superior to any other vasoconstricting agent. On this account it would seem that there is every justification for continuing to use pressor drugs in the treatment of certain types of circulatory collapse.

CONCLUSIONS

The state of shock or collapse is occasioned by a disproportion between the blood volume and the capacity of the vascular bed. This disproportion may be brought about by a diminution of the blood volume, or by dilatation of the peripheral vessels, or, as in many cases, by both factors acting simultaneously. The most important single factor in correcting this disproportion is the early and adequate restoration of blood volume by blood transfusion. The second factor is the reduction of the capacity of the vascular bed by means of noradrenaline. Ideally the best method is to administer both simultaneously, but in many cases blood is not immediately obtainable. In these cases noradrenaline when administered alone may tide the patient over a dangerous period.

SUMMARY

The introduction of noradrenaline is a marked therapeutic advance in the treatment of acute hypotension in surgical cases. It has been used as follows:

(*a*) as a means or resuscitating severely shocked patients in the pre-operative phase,

(*b*) during operation to resuscitate cases with a falling blood pressure not responding to blood transfusion, and

(*c*) in cases of post-operative collapse due to peripheral circulatory failure.

In the above three groups of cases very good results have been obtained.

It has also been used in cases of profuse haemorrhage. The results here are equivocal but are encouraging and merit further study.

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REFERENCES

Bacq, Z. M. (1934). *Ann. Physiol. Physicochim. biol.*, **10**, 467.

Barlow, M., Ginsberg, H., and Sottleck, J. (1953). *S. Afr. med. J.*, **27**, 564.

Bergmann, H. (1952). *Wien. med. Wschr.*, **102**, 488.

Cahill, G. F., and Monteith, J. C. (1951). *New England J. Med.*, **244**, 657.

Cappe, B. E., and Pallin, T. M. (1951). *Anesthesiology*, **12**, 728.

Chippeaux (1954). (Quoted by Laborit, H., and Huguenard, P. (1954).)

Churchill-Davidson, H. C. (1951). *Brit. med. J.*, **2**, 1951.

—— Wylie, W. D., and Miles, B. E. (1951). *Lancet*, **2**, 803.

Crawford, E. S., and Haynes, B. W. (1953). *Amer. J. Surg., Baltimore*, **19**, 191.
Crumpton, C. W., Murphy, R. R., Wittmore, J. J., Copps, R. T., and Orth, O. S. (1952). *Fed. Proc.*, **11**, 335.
Euler, U. S. von (1946). *Acta physiol. scand.*, **12**, 73.
Goldenberg, M., Pines, K. L., Baldwin, E de F., Greene, D. G., and Roh, C. E. (1948). *Amer. J. med.*, **5**, 792.
—— Apgar, V., Deterling, R., and Pines, K. L. (1949). *J. Amer. med. Ass.*, **140**, 776.
MacKay, E. M., and Pecka, E. F. Jr., (1950). *Proc. Soc. exp. Biol.*, N.Y., **75**, 245.
Laborit, H. (1950). *Pr. méd.*, **58**, 138.
Laborit, H., and Huguenard, P. (1951). *Pr. Méd.*, **59**, 1329.
—— —— (1954). *Practique de L'hibernotherapie*, Masson & Cie: Paris.
Livesey, W. K., and Chapman, D. W. (1953). *Amer. J. med. Sci.*, **225**, 159.
Nicol, Mattei, Brun-Buisson, Francois, Jaffry, and Lagneau (1953). *Mem. Acad. Chir. Paris*, **79**, 392.
Swan, H. J. C. (1951). *Brit. med. J.*, **1**, 440.
—— (1952). *Brit. med. J.*, **1**, 1003.
Wells, C., and Gray, T. C. (1952). Chapter in *Prostatectomy*. Livingstone: Edinburgh.
—— (1953). *Modern Trends in Urology*, ed. by E. W. Riches. Pp. 165–278. Butterworth: London.
Wyman, J. B. (1953). *Proc. R. Soc. Med.*, **46**, 605.

FACULTY NEWS

DEPARTMENT OF ANAESTHETICS

The work of building the new Department is rapidly progressing, and it is confidently anticipated that it will be available for use in about eighteen months time.

Meanwhile, energetic steps are being taken to raise the money for the upkeep of the Department which is estimated at £12,000 a year. So far the Faculty has received grants totalling £6,000 a year under covenant for seven years. It is confidently anticipated that further substantial gifts will be forthcoming in the near future.

NUFFIELD PRIZE

Dr. Noel Morris Cass, of Melbourne, who obtained the highest marks in the recent Primary F.F.A.R.C.S. Examination, has been awarded the Nuffield Prize.

BRITISH COUNCIL

The Faculty is arranging with the British Council to hold a short course in Anaesthetics for European doctors. This will be held from February 28 to March 12, 1955.

BOOK REVIEW

Die Zentralnervösen Wirkungen von Heilmitteln. By E. Rothlin. Published by Georg Thieme Verlag. Stuttgart, 1954. Pp. 39.

This little booklet on the effect of drugs on the central nervous system, is the text of a public lecture delivered by a senior pharmacologist of one of the large Swiss pharmaceutical firms.

The phenomena of anaesthesia are described, but in an elementary manner, and this section would be of little interest to anaesthetists. The rest of the lecture deals with a variety of drugs mainly of interest to neurologists and psychiatrists. For example, ergotamine is recommended for that peculiar Swiss complaint, Foehn headache, while the hypotensive effects of Hydergin are described. There is also a short but interesting account of the peculiar drug known as L.S.D. —another ergot derivative—which is said to produce "optic hallucinations" and "de-personalization". Non-medical scientists would probably find this lecture interesting.

W. W. Mushin

Brit. J. Anaesth. (1955), **27**, 40.

ANNOTATIONS

CLINICAL INVESTIGATIONS

WHAT is a clinical investigation? At one end of the scale are teams of professional research workers, much money, many patients, large laboratories, great organization. At the other end, some single individual responding for the first time to the urge to find out for himself the answer to some simple clinical problems. This beginner observes, records, thinks, and soon finds the subtleties of Nature too much for him.

The lucky beginner can profit from the advice of an expert colleague. The less fortunately placed enthusiast must teach himself. Happily there is for him nowadays a wide choice of reading matter. This he can grade to suit his increasing knowledge. Bradford Hill (1948), Mainland (1938), Bernstein and Wetherall (1952), Moroney (1951) are but a few of those who will start him off and see him along the right path. The first chapters of Fisher's (1951) classic, *The Design of Experiments*, will whet his appetite for more. Perhaps in one experiment there described, that of the lady who claims she can tell whether the milk or the tea was put into the cup first, he will see a parallel to one of his own problems, and thereby find a way to a correct solution. But the later, more difficult, chapters of this book he will avoid, for the time being.

If the fires of his enthusiasm need fanning Dale (1950), Green (1954), Arnott (1948), and Ryle (1947) will be among those to do it. Bradford Hill (1951) and Ross (1951) will give him some more general advice. Ting (1951) will impress on him the importance of biometry in anaesthesia, and Denton and Beecher (1949) or Cohen and Beecher (1951) will, for example, provide him with a clear plan of attack on a specific problem.

When he finds things getting too difficult he will refresh himself with Huff's (1954) recent publication. Here with the "Gee-Whiz Graph", "The Little Figures That Are Not There", and "Post Hoc Rides Again" he will laugh, not only at his own mistakes but at those of others, and benefit in many ways whilst so doing.

Towards the end of this reading, and all the further reading which it has led him to, he may pause to wonder why, as a qualified doctor, he was at first so ignorant. Why had he not been *taught* more? He may come to think that the remark "What!! Statistics in the Medical Curriculum?" might well be replaced by "What Statistics in the Medical Curriculum?" (Hill, 1947).

REFERENCES

Arnott, W. M. (1948). "Clinical Research in the Education of the Specialist", *Lancet*, **2**, 441.

Bernstein, L., and Weatherall, M. (1952). *Statistics for Medical and other Biological Students.* London: Livingstone.

Cohen, E. N., and Beecher, H. K. (1951). "Narcotics in Preanaesthetic Medication", *J. Amer. med. Ass.*, **147**, 1664.

Dale, H. (1950). "Scientific Method in Medical Research", *Brit. med. J.*, **2**, 1185.

Denton, J. E., and Beecher, H. K. (1949). "New Analgesics", *J. Amer. med. Ass.*, **141**, 1051, 1146.

Fisher, R. A. (1951). *The Design of Experiments.* 6th edition. London: Oliver and Boyd.

Green, F. H. K. (1954). "The Clinical Evaluation of Remedies", *Lancet*, **2**, 1086.

Hill, A. B. (1948). *Principles of Medical Statistics.* 4th edition. London: Lancet.

—— (1951). "The Clinical Trial", *Brit. med. Bull.*, **7**, 278.

—— (1947). "Statistics in the Medical Curriculum?", *Brit. med. J.*, **2**, 366.

Huff, D. (1954). *How to Lie with Statistics.* London: Gollancz.

Mainland, D. (1938). *The Treatment of Clinical and Laboratory Data.* London: Oliver and Boyd.

Moroney, M. J. (1951). *Facts from Figures.* Harmondsworth: Penguin Books.

Ross, O. B. (1951). "Use of Controls in Medical Research", *J. Amer. med. Ass.*, **145**, 72.

Ryle, J. A. (1947). "The Meaning of Normal", *Lancet*, **1**, 1.

Ting, K. S. (1951). "The Importance of Biometry in Anesthesiology", *Anesthesiology*, **13**, 1.

Brit. J. Anaesth. (1955), **27**, 41.

DIFFUSION ANOXIA

ANY new work relevant to anoxia and its aetiology should receive serious consideration by anaesthetists. The original classification of anoxia into three types by Barcroft (1914) and eventually into four by Peters and Van Slyke has held the field up to the present, although there have been many authors who have modified or added to it. Saklad (1953), for example, distinguished seven categories, namely:

(1) *Atmospheric*, where there is a reduced partial pressure of oxygen in the inhaled atmosphere.

(2) *Tidal*, in which the aetiology is a decreased minute volume of respiration.

(3) *Alveolar*, following a reduction in the efficiency or number of functioning alveoli.

(4) *Haemoglobic*, equivalent to Barcroft's anaemic.

(5) *Stagnant*.

(6) *Histotoxic*.

(7) *Anoxia* of demand, when the metabolism of the tissues is abnormally high.

These categories still do not take into consideration the important acarbic anoxia to which attention has been drawn by Pask (1945), due to a shift to the left of the oxyhaemoglobin dissociation curve brought about by a reduction in the carbon dioxide content of the blood.

Now is described "Diffusion Anoxia" (Fink, Carpenter and Holaday, 1954; Fink, 1954) which may occur during recovery from nitrous oxide anaesthesia.

During anaesthesia with nitrous oxide, some 25–30 l. of the gas may accumulate in the body tissues and evidence is presented to show that during the early minutes of recovery after cessation of administration of the gas, nitrous oxide may diffuse into the alveoli "in such volume as to constitute 12 per cent of the expired atmosphere". Fink (1954) has shown that this may dilute inspired air, reduce the partial pressure of oxygen in the alveoli, and can thus reduce the arterial oxygen saturation. While this is not of serious consequence to the majority of patients who are well able to tolerate such a mild degree of oxygen lack, it may be of some importance in patients who have little cardio-pulmonary reserve, as, for example, those with myocardial disease, or who have undergone pneumonectomy.

While theoretically this diffusion in the alveoli will occur after the administration of any anaesthetic gas, clearly those less soluble in blood and tissues than nitrous oxide will diffuse out very much more slowly and there will be only an insignificant dilution of the inspired air.

It is suggested, in order to avoid this period of hypoxia, that in poor-risk patients, and especially in those who have had some reduction of the pulmonary ventilatory capacity, it is advisable to administer pure oxygen for several minutes at the end of a nitrous oxide anaesthetic.

The disturbance caused by this diffusion of nitrous oxide is, in fact, only a form of anoxic anoxia, and the recognition of this phenomenon, important as it undoubtedly is, would not seem to justify the addition of another type to the well-tried Barcroft classification.

REFERENCES

Barcroft, Sir J. (1914). *Respiratory Function of the Blood.* 1st Ed. Cambridge University Press.

Fink, B. R., Carpenter, S. L., and Holaday, D. A. (1945). *Fed. Proc.*, **13**, 354.

Fink, B. R. (1954). *Acta anaesth. Belg.*, **5**, 42.

Pask, E. A. (1948). *Ann. R. Coll. Surg., Engl.*, **2**, 24.

Saklad, M. (1953). *Inhalation Therapy and Resuscitation.* Oxford: Blackwell Scientific Publications.

ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.

Licentiate of the Royal College of Physicians

(*Continued from Vol. XXVI, page* 441)

CIRCUMSTANCES WHICH INFLUENCE OR MODIFY THE EFFECTS OF CHLOROFORM

I arrived at the conclusion, after much careful observation, that chloroform might be given with safety and advantage in every case in which the patient requires, and is in a condition to undergo a surgical operation; and having acted on this conclusion for several years, I have found no reason to change it. It is desirable, however, to pay attention to every circumstance connected with the health and constitution of the patient before exhibiting chloroform, as many of these circumstances influence its effects.

Age. The age of the patient has considerable influence in modifying the effects of chloroform. It acts very favourably on children: they sometimes oppose the inhalation of it as long as they are conscious, but it does not occasion the rigidity and struggling after loss of consciousness, which are sometimes met with in the adult. Anæsthesia is generally induced with a less amount of narcotism of the nervous centres in children than in grown up persons. The effects of chloroform are more quickly produced and also subside more quickly in children than in adults, owing no doubt to the quicker breathing and circulation. It often happens, however, that when the insensibility has been kept up for some time, say twenty minutes or half an hour, in a child, it is followed by a natural sleep of a few hours' duration, provided there is no painful wound, or other cause, to prevent the sleep. I have given chloroform in a few cases as early as the ages of eight and ten days, and in a considerable number before the age of two months; and I have at this time, June 30th, 1857, memoranda of the cases of 186 infants under a year old to whom I have administered this agent. There have been no ill effects from it either in these cases, or in those of children more advanced in life; and it is worthy of remark that none of the accidents from chloroform which have been recorded, have occurred to young children.

There is nothing peculiar in the effects of chloroform on people advanced in years, except that its influence subsides rather slowly, on account of the slower breathing and circulation. I have given chloroform to many patients over seventy-five years of age, and to one as old as ninety years.

Strength or Debility. The comparative strength or debility of the patient has considerable influence on the way in which

chloroform acts. Usually the more feeble the patient is, whether from illness, or any other cause, the more quietly does he become insensible; whilst if he is strong and robust, there is very likely to be mental excitement in the second degree, and rigidity of the muscles, and probably struggling in the third degree of narcotism. Patients in a state of debility resemble children, not only in coming quietly and easily under the influence of chloroform, but also in the circumstance, that the common sensibility is suspended with less narcotism of the nervous centres than is generally required in robust persons. Children and persons in a state of debility have usually an acute sensibility which causes them to suffer pain from very slight injuries, but this sensibility is more easily suspended by chloroform than the less acute sensibility of robust persons. It is in strong men, accustomed to hard work or athletic sports, that the rigidity and struggling previously alluded to in describing the effects of chloroform, most frequently occur after the loss of consciousness. Some of the patients in whom the struggling and rigidity have been greatest were gentlemen belonging to boating clubs; but I think the patient in whom these symptoms were most violent, was a celebrated harlequin of one of the London theatres, on whom Mr. Fergusson operated a few years ago.

The persons in whom the rigidity and struggling are well marked are often lean and wiry, and these symptoms rarely occur in fat people. The rigidity and struggling are less marked when the chloroform is given slowly than when quickly given.

Hysteria. Patients who are subject to hysteria sometimes have symptoms of the complaint, such as sobbing, crying, or laughing, as soon as consciousness is suspended, or even impaired, by the chloroform; but these symptoms can always be subdued by proceeding with the inhalation. In a very few instances the hysterical state returns, and becomes troublesome as the effect of the vapour subsides. In two or three cases that I have met with, it continued for three or four hours, but it usually subsides in a much shorter time. The inhalation should not be suspended on account of the hysteria, but should be continued till it is subdued before an operation is performed.

I have rarely seen a decided fit of hysteria from the effects of chloroform, but in the case of a young married lady, to whom I gave this agent to prevent the pain of an operation on the rectum, a somewhat violent paroxysm of hysteria came on directly after the inhalation was commenced. The surgeon would not permit me to continue the chloroform, and expressed his intention of operating without it. After waiting for about half an hour, however, for the hysteria to subside, and finding that it continued the same as at first, the inhalation was resumed. The patient was soon rendered insensible, and lay perfectly still whilst the operation was performed. There was a little hysteria as the effects of the chloroform subsided, but not so severe as before.

I have several times seen hysterical symptoms in the male, either during the administration of chloroform, or whilst the patient was recovering from its effects. But in all these cases the patients informed me afterwards that they were subject to hysterics when under the influence of mental emotion.

In some persons who are subject to hysteria, the breathing becomes excessively deep and rapid whilst inhaling chloroform. This usually occurs just as the patient is becoming unconscious, but in a few cases even earlier, and the patient is aware of the impulse to breathe in this manner. After this kind of hysterical breathing has lasted a minute, the patient generally rests nearly a minute without breathing at all, after which the respiration generally becomes nearly natural. I give the chloroform very sparingly during this violent breathing, or else withdraw it altogether for a minute or two.

I do not consider that the hysterical diathesis forms any objection to the use of chloroform in operations, as the patients would be generally quite as liable to suffer an attack of hysteria from the pain, if chloroform were not used.

Epilepsy. Chloroform occasionally brings on a fit of epilepsy in persons who are subject to this disease. It was stated in one of the foreign medical journals, in 1848, that this agent was so certain to cause a fit in epileptic persons, that it might be used to detect impostors pretending to be subject to this disease; but if this assertion has been acted on, it must have led to great injustice, for I have many times administered chloroform to the extent of causing complete insensibility in epileptic patients who required to undergo operations, without its inducing the least approach to a fit.

In the few cases in which epileptic convulsions are occasioned by chloroform, they do not appear till the third degree of narcotism is induced, in this respect differing from hysteria, which comes on in the second degree, or even earlier, as was stated above. The course to pursue, when epileptic convulsions appear, is to continue the chloroform steadily and gently till they subside. I have never seen the chloroform fail to subdue the convulsion in a very few minutes, and I have never seen them recur after the operation, as the effects of the vapour subsided. In medical and obstetric practice, and for slight operations, it is not requisite to carry the effects of chloroform so far as that stage in which an epileptic fit would occur, so that under these circumstances the fact of a patient being subject to epilepsy hardly requires to be taken into account.

Pregnancy. I have repeatedly given chloroform at all periods of pregnancy, both for tooth drawing and more important operations, and I have not met with any ill effects from it in any of the cases.

The Menstrual Period. It is customary to avoid the menstrual period in fixing the time for a surgical operation, when it can be so arranged. There are, however, often reasons for not waiting over this period, and under such circumstances, I do not know any objection to the inhalation of chloroform. I have administered it frequently during the menstrual period, and have seen no ill effects from it. I have observed that there is a little more tendency to slight hysterical symptoms, during its inhalation at this period, than when the same patients inhale it at other times, which is what we might expect.

Diseases of the Lungs. Affections of the lungs sometimes cause a little difficulty and delay in the administration of chloroform, as the vapour is liable to excite coughing when the mucous membrane of the air passages is irritable. The inconvenience is, however, confined to the time

of inhalation, for the cough is generally relieved afterwards.

I have given chloroform for surgical operations in many cases where phthisis was present, and in several patients who had suffered from hæmoptysis, and have not seen any ill effects from its use in these cases. Chloroform has indeed often been inhaled with advantage to relieve the cough in consumption. The cases of chronic bronchitis in which chloroform is administered for surgical operations are still more numerous. The effects I have observed have been coughing at the time of inhalation, and very often a relief of the cough afterwards. Some of the patients had emphysema of the lungs. It is scarcely necessary to allude, in this place, to acute diseases of the lungs, as surgical operations are not performed during their continuance, but from the fact of chloroform being inhaled occasionally in the treatment of these affections, it is evident that they would cause no obstacle to its employment.

Disease of the Heart. There is a very general impression that the use of chloroform is unsafe when disease of the heart exists, more particularly, fatty degeneration of that organ. This belief has been encouraged by the circumstance that this affection has been present in a few of both the real and alleged deaths from chloroform; and also by the fact that in the accidents that have been really due to chloroform, the heart has been the organ on which it has exerted its fatal influence. When we come to investigate these cases, however, we shall find reason to conclude that the heart has probably been diseased in quite as great a proportion of the patients who have taken chloroform without ill effects, as in those who have succumbed under its influence. As regards my own practice, indeed, the only case in which death could in any degree be attributed to the chloroform, was one in which there was extreme fatty degeneration of the heart; but, on the other hand, I have given chloroform in numerous cases without ill effects where the symptoms of this, as well as other affections of the heart, were present in a very marked degree. Indeed, I have never declined to give chloroform to a patient requiring a surgical operation, whatever might be his condition, as I early arrived at the conclusion that this agent, when carefully administered, causes less disturbance of the heart and circulation than does severe pain. Whenever I have had an opportunity of seeing an operation performed without chloroform, I have carefully observed the pulse, and although none of these operations have been of a very severe nature, I have found the circulation to be much more disturbed than it would have been by chloroform carefully administered. The pulse in most of these cases has been excessively frequent during the operation, and in some instances it has intermitted to an unusual extent.

In one instance, I had an opportunity of witnessing a similar operation on the same patient, first without chloroform, and afterwards under the influence of this agent. On January the 6th, 1855, Mr. Fergusson performed lithotrity, in King's College Hospital, on a man, aged fifty-one. He generally directs chloroform to be administered in lithotrity, but in this instance he omitted to do so, as he thought that the bladder was not very irritable, and that the patient would not suffer

much. I began to feel the pulse just when the patient saw the lithotrite about to be introduced. It was 120 in the minute. As soon as the instrument was introduced, the pulse increased to 144, and immediately afterwards it became uneven, irregular, and intermitting. I could not count more than three or four beats at a time; and, occasionally, when the pain seemed greatest, and the man was straining and holding his breath, the pulse was altogether absent for four or five seconds. In order to ascertain whether the absence of pulse at the wrist might not depend on the pressure of the muscles of the arms, caused by grasping the table, I applied my ear to the chest, and found that there was no sound whatever to be heard during the intervals when the pulse was imperceptible. It was evident that the patient held his breath till the right cavities of the heart became so distended as to stop the action of that organ till the respiration returned. The man did not complain or cry out during the operation. A week afterwards the lithotrity was repeated, but on this occasion I administered chloroform. The pulse was about 120 in the minute when the patient began to inhale the chloroform, but it became slower as he was made unconscious, and it was regular and natural during the operation. It was only towards the end of the operation, when the effect of the chloroform was allowed to diminish, and when the man began to strain a little, though not yet conscious, that the pulse intermitted slightly, passing over a single beat occasionally. There were none of the long intermissions of the pulse observed on the former occasion.

It is very evident that if the abovementioned patient had been the subject of any affection of the heart which weakened or embarrassed its action, he would have run a much greater risk from the pain of the first operation, than from the inhalation of chloroform in the second one.

In a few of the patients having the arcus senilis of the cornea, a weak, intermitting, or irregular pulse, and other signs of fatty degeneration of the heart, there have been a feeling of faintness and a tendency to syncope, as the effects of the chloroform were subsiding, especially when the operation had been performed in the sitting posture; but these symptoms have soon subsided, in all the cases I have met with, on placing the patient horizontally, with or without the help of a little ammonia to the nostrils.

(*To be continued*)

CORRESPONDENCE

Sir,—I would like to make some comments on the article by Woolmer and Lind in your September issue, and on some of the remarks in your annotation.

Woolmer and Lind are unjustified in concluding that the "modification of Magill's attachment" described by me (Bullough, 1952) decreases its efficiency in eliminating CO_2, since they do not give figures for an actual Magill attachment as used clinically. A spring-loaded expiratory valve behaves quite differently from a glass tube submerged under water.

The duration of inspiration, expiration, and pause in their experiment is unfortunately not given. This affects the concentration of CO_2 in the inspired mixture.

In clinical anaesthesia a change from a semi-closed to my T-piece circuit almost invariably results in a decrease in respiratory activity. It is therefore hard to believe that a great (sixfold) increase in the concentration of CO_2 in the inspired mixture takes place. The chief value of T-piece technique lies in the absence of resistance to expiration; is it possible that this alone accounts for the reduction in respiratory activity?

I have, as it happens, made a modification of my technique whereby this possible disadvantage is removable. The modification awaits publication.

One wonders if Woolmer and Lind's experiments have any clinical application. My table shows that, after twenty minutes clinical anaesthesia with $N_2O + O_2$, Swartz, Adriani and Mih (1953) found a concentration of CO_2 in the inspired mixture twenty times higher than those obtained with Woolmer and Lind's experimental machine. This is rather a large difference, even though a slightly different semi-closed circuit was used, and, of course, a face-mask.

Your annotator's calculations (p. 344) based on an average inspiratory flow of twice the minute-respiratory-volume ($2 \times$ MRV) are invalid. The normal inspiratory flow-rate has been found to be five or six times the MRV. Orkin *et al.* (1954) give references to this.

He mentions on the same page an arbitrary allowable maximum of 0.2 per cent CO_2 in an inspired mixture. This is unrealistic. My table shows that even conscious volunteers having received no respiratory depressant drugs and breathing air, are unable to prevent a concentration of 0.9 per cent CO_2 in the inspired mixture.

Table showing CO_2 concentrations found in the inspired mixture in semi-closed circuits: 8 l./min. fresh gas-flow.

Authors	Methods	CO_2 concentration in inspired mixture (per cent)
Woolmer and Lind	Machine simulating patient	0.11
Swartz, Adriani and Mih	Conscious volunteers breathing air, no drugs given	0.9
As above	Clinically anaesthetized subjects, breathing nitrous oxide-oxygen or ethylene-oxygen mixture:	
	(*a*) after 10 minutes anaesthesia	1.25
	(*b*) after 20 minutes anaesthesia	2.5

On p. 345 your annotator refers to the "Simple T-piece" used in Woolmer and Lind's experiments as an *Ayre's T-piece*. Ayre's T-piece technique bears little resemblance to the simple T-piece used, and would certainly not give such bad figures for inspired CO_2. I submit that Dr. Ayre's name should not be associated with these bad figures.

When I described my T-piece technique, I recommended, for maintenance, a fresh gas flow of 8 l./min. In the correspondence which followed, the flow rate was criticized as being too

high. I gave my reasons for using a flow of 8 l./min. in any semi-closed circuit (without CO_2 absorption). This figure was based primarily on clinical observation. Now mathematical calculations suggest the flow may be too low. The important thing, however, is the clinical result. I am not yet persuaded to alter my flow-rate, though I do, of course, occasionally use higher flows for a short time when indicated.

In clinical practice the concentration of CO_2 in the alveoli is more important than that in the inspired mixture.

The problem of the optimum concentration of CO_2 in the inspired mixture remains unsettled.

JOHN BULLOUGH,
Dartford, Kent

REFERENCES

Bullough, J. (1952). *Brit. med. J.*, **1**, 28.
Orkin, L. R., Siegel, M., and Rovenstine, E. A. (1954). *Cur. Res. Anesth.*, **33**, 217.
Swartz, C. H., Adriani, J., and Mih, A. (1953). *Anesthesiology*, **14**, 437.

Sir,—The excellent article by Dr. E. Harvey Franks on "Anaesthesia for Intra-nasal and Intra-oral Operations" has many interesting and practical details, but I feel that one point needs amplification.

Under the heading "Results", he states that "a number of patients had a sore throat from the pharyngeal pack". But he gives no details of the technique of pharyngeal packing.

At one time it was my practice to pack the pharynx using a tongue depressor and the indirect lighting of the anaesthetic room and inserting the gauze into the pharynx with Magill's endotracheal forceps. In spite of lubricating with vaseline or liquid paraffin, a large number of patients complained of sore throat post-operatively. I confess that I looked on this as an inevitable complication until one day an E.N.T. colleague showed me in one of my patients marked abrasions on the palate. Finding this condition in several others, I realized that my technique was at fault.

Now I make use of the curved blade of Mackintosh's laryngoscope to obtain direct lighting of the pharynx and am able to insert the pack without touching the palate or fauces. With this careful technique, sore throat is a rare complication and when it occurs, I blame myself for packing too tightly.

I hope you will think this letter deserving of publication, as there may be others who do not know of this easy way of packing atraumatically.

DONALD BLATCHLEY
Chiswick

THE SHEFFIELD AND EAST MIDLANDS SOCIETY OF ANAESTHETISTS

THE Annual General Meeting of the above Society was held at the City General Hospital, Nottingham, on May 29, 1954, when the following officials were elected:

President:	Dr. W. J. Patterson (Sheffield).
Vice-President:	Dr. H. E. Pooler (Chesterfield).
Treasurer:	Dr. J. P. Hope (Sheffield).
Secretary:	Dr. C. A. S. Hamilton (Sheffield).
Committee:	Dr. James Johnston (Sheffield). Dr. A. C. Fraser (Lincoln). Dr. F. Logan Turner (Leicester).

There are now 62 Members and 9 Associate Members, the latter being junior anaesthetic staff of various hospitals in the region.

The Annual Dinner of the Society was held at the George Hotel, Nottingham, on Thursday, October 21, 1954, at which there was present a large number of members and their guests.

After an excellent repast, Dr. R. W. Cope gave an interesting and instructive address entitled "Anaesthesia on Children: The Present and Future", which was much appreciated by his audience.

PROGRAMME 1955

March 25: Registrar's Paper to be read at Nottingham.

May 21: Annual General Meeting to be held at Lincoln.

Hon. Secretary: C. A. S. HAMILTON,
43 Montgomery Road, Sheffield 7.

Educational Supplement

January 1955

ON THE MODE OF ACTION OF ANAESTHETICS

BY

G. A. MOGEY

Department of Pharmacology, University of Leeds

SOME of the hypotheses about the mode or modes of action of anaesthetics are nearly as old as anaesthesia itself. Indeed, they are among the earliest speculations about the mechanism of drug action but, although much work has been done to elucidate the fundamental changes, there is still no general agreement and no universally accepted theory. Many of the older hypotheses are no more than descriptions or superficial explanations of phenomena accompanying anaesthesia and most can be incorporated into the more general and more basic ideas of today.

Ignoring the problems of absorption and transport—which are, in fact, relatively simple when compared with those of the mode of action—one can say that anaesthetics must act either inside the nerve cell or at its surface or both.

THEORIES BASED ON INTRACELLULAR CHANGES

Coagulation and flocculation. The suggestion of Claude Bernard (1853) that narcotics affect the stability of cell colloids, is not now accepted to be the basic mechanism of anaesthesia. Neither is it very informative. He believed that a narcotic coagulated cell colloids and that the change was reversed on withdrawal of the drug. Since the reversible nature of anaesthesia has to be explained in any acceptable theory, recovery was supposed to be due to peptization of the proteins no longer under the influence of the anaesthetic. Bernard (1875) eventually went even further and claimed that all anaesthetics act by this one mechanism. His main experimental evidence was that muscle exposed to chloroform or ether became opaque.

Much later, in 1931, it was shown, by Bancroft and Richter that such coagulation—or rather flocculation—could, indeed, be observed under the microscope *in vitro*. The concentrations of anaesthetic necessary to produce this are however, usually higher than those required for anaesthesia. Furthermore, the coagulation is often irreversible; all substances that reduce the stability of colloids are not narcotics; cyclopropane, ethylene and nitrous oxide—all well-known anaesthetics—have little ability to produce aggregation in colloids (Krantz and Carr, 1954) and flocculation occurring in anaphylaxis does not lead to narcosis. Anyhow, the theory of colloidal aggregation or precipitation sheds no light on how such a change affects the cell nor does it enable reliable predictions to be made.

Further evidence in favour of this theory was, however, provided recently when it was shown that the effects of narcotics on bacteria can be antagonized by high pressure. This led Johnson and his colleagues (1942) to argue that narcotics act by denaturing protein; when denaturation occurs volume increases, and it is this increase in volume, and the consequent denaturation, which the high pressure prevents.

Lipoid transfer. The earliest of all the theories is that of von Bibra and Harless (1847) who, noting that nearly all fat solvents are good narcotics, suggested that narcosis was due to the removal, by the anaesthetic agent, of fatty material from the nerve cells; the fat was supposed to be deposited temporarily in the liver. They claimed that ether, being a good fat solvent, could carry lipoids from brain to liver. This theory cannot account for rapid recovery from anaesthesia for, after the anaesthetic has left the body, how could the lipoid be carried back to the brain with sufficient speed?

This unconvincing theory of Bibra and Harless, although never accepted, attached early importance to the brain lipoids which, since then, have been continuously implicated in one hypothesis or another. The high sensitivity of the brain, formerly associated with its great blood supply, is often accredited to their presence.

The Meyer-Overton law. The brain lipoids are also implicated in the much later postulates of Meyer (1899) and Overton (1901). They believed that all fat-soluble, chemically indifferent substances should act as anaesthetics, that such substances should first and most markedly affect cells with a high lipoid content, and that the potency, of certain types of substance at least—for Meyer (Meyer, 1937) limited himself to the "indifferent", or aliphatic, narcotics—should be directly related to the ratio of the affinity of the agent for lipoid to its affinity for water. The last of their postulates has come to be known as the Meyer-Overton law—the greater the degree of solubility of the anaesthetic agent in lipoid over that in water, the greater the potency of the anaesthetic.

Meyer emphatically excluded narcosis from magnesium for he did not agree with Bernard's unitarian theory of the mode of action of all anaesthetics. For their experimental work Meyer and Overton, who discovered the law independently and almost simultaneously, used a biphasic system of oil and water, choosing olive oil as a simple and easily available substitute for the brain lipoids although they realized that this was an over-simplification. Adherents to their theory—if it can be called a theory—were wont to invoke this difference to explain away any divergence from the law.

The theory has been much criticized, but the oft-quoted discrepancy between the oil/water distribution coefficient of chloral hydrate and its anaesthetic potency is no longer an acceptable criticism, for it is probable that trichloroethanol, to which chloral hydrate is converted in the body, is the active material. Meyer's son (Meyer and Hemmi, 1935; Meyer, 1937) has found that there is better correlation when oleic alcohol is used instead of olive oil. Although the solvent properties of oleic alcohol are very like those of the brain lipoids, it is probable that the orientation of the lipoid molecules at the

surface of the nerve cell is such that the solvent properties of an unorganized fatty substance bear little relation to those of the cellular lipoid. One of the greatest limitations of the Meyer-Overton postulates is that they only apply to aliphatic narcotics, giving, beyond this, no indication as to when a new drug should be expected to obey the law

Ferguson's principle. To avoid inferring the solubility of an anaesthetic in brain lipoids from its solubility in olive oil, or some other probably inadequate substitute, Ferguson, in 1939, proposed a new principle. He argued that if an anaesthetic is in equilibrium between any two phases, its thermodynamic potential must be identical in each. If this potential can be measured in only one of the phases, it is, therefore, automatically known for the inaccessible phase. Ferguson has given details of how to calculate this activity, and has done the calculation for a number of narcotic substances, finding that the thermodynamic activities of a diverse group of anaesthetics lie close together. He therefore suggested that the thermodynamic activity is closely related to the anaesthetic potency of a drug, provided that the mechanism of anaesthesia is physical and not chemical.

Richet's rule. Ferguson's principle leads to the conclusion that anaesthetic potency is inversely proportional to solubility in water (Butler, 1950), a conclusion which is the same as the well-known rule of Richet (1893). No one has yet explained how a negative property like insolubility in water might produce anaesthesia. The differences in anaesthetic potency, moreover, between enantiomorphic forms of some drugs, show clearly that physical properties alone cannot always account for the narcosis. It may be, of course, that some drugs act by physical and others by a chemical mechanism.

Chemical combination. An obscure hypothesis by Moore and Roaf (1904, 1905)—who, incidentally, did much to discredit the coagulation theory—has suggested vaguely that the anaesthetic upsets cellular metabolism by combining with some of the intracellular constituents. If this implies a chemical type of reaction it is not likely to be true, for such a diverse group of substances as the anaesthetics can hardly be expected to produce a single kind of chemical reaction in the cell. One must remember, however, that the widely varied antibiotics nearly all produce the same end-result in bacterial cells—inhibition of protein synthesis—and that they do so by different mechanisms. Incidentally, Meyer stressed that different drugs having different primary points of attack might nevertheless bring about the same end-result. It is generally considered more likely that the action of an anaesthetic on a brain cell is of a physical rather than of a chemical nature. Moreover, if there is a chemical interaction between cell constituents and the anaesthetic it becomes more difficult to picture the subsequent release of the anaesthetic in an unaltered form, for most inhalation anaesthetics are excreted unchanged.

Asphyxial mechanisms. The processes of oxidation within the cell are disorganized by anaesthetics and the theory that anaesthesia is due to such an asphyxial mechanism was first propounded by Ver-

worn in 1909. Although the concentrations used experimentally were too high to make it possible to agree that a similar mechanism applies in clinical practice, further evidence has suggested that the basic change may be connected in some way with interference in oxidative processes. Using brain slices, Quastel and Wheatley (1934) have shown that high normal anaesthetic concentrations are capable of producing a reversible inhibition of oxidation.

The adherents to this theory attach great importance to the discovery by Keilin (1925) that ethyl urethane inhibits the reduction of cytochrome, a discovery which emphasizes the importance of the dehydrogenases in the production of narcosis. It is suggested that anaesthetics prevent some factor—probably a flavoprotein—acting as a hydrogen carrier between pyruvic dehydrogenase and cytochrome oxidase. The brain is supposed to be especially sensitive to anaesthetics because it is particularly dependent upon carbohydrate metabolism.

There are many arguments against this interesting theory. The relationship between the degree of *in vitro* inhibition of oxidation and the depth of anaesthesia remains vague. Concentrations of ether (Jowett and Quastel, 1937) and ethanol (Jowett, 1938) that produce slight depression of the central nervous system have no demonstrable effect *in vitro* on brain tissue respiration; and certain drugs that produce marked inhibition *in vitro*—picrotoxin (Klein, 1943), mescaline and indole (Quastel and Wheatley, 1933), for instance—fail to produce anaesthesia, indeed two of these are convulsants. Although the oxidative inhibition is usually reversible, it is permanent with ether and ethanol. Furthermore, the rate at which the *in vitro* inhibition appears does not always agree with the rate of development of narcosis *in vivo*.

Because of these and other arguments it is considered by many that the decreased oxidation, which undoubtedly occurs, may really be a result rather than the cause of the anaesthesia.

THEORIES BASED ON AN ACTION AT THE CELL SURFACE

The discovery of the role of the polarized surface of nerve cells and the brief reversal of the polarity during activity and conduction, by the passage of sodium ions inwards and potassium ions outwards through that surface, has naturally led to speculation about the action of anaesthetics at such a site.

Surface tension. The first theory directly concerned with the membrane of the nerve cell was that of Traube (1904). He suggested that the activity of an anaesthetic resulted from its ability to lower the surface tension of water at an air/water boundary and that narcotic potency was directly related to this. An air/water boundary is, however, far too simple a model for the cell surface. It has, furthermore, been shown that some narcotics have no action on the surface tension of an air/water interface; for example, methane and nitrous oxide have no such effect but are quite potent narcotics. Later Höber (1907, 1945), Lillie (1909) and Warburg (1921) modified and extended this theory. Höber suggested that adsorption of the anaesthetic at the cell surface decreased permeability: this would interfere with the free passage of

ions and so would prevent depolarization. Lillie produced evidence of a decreased permeability in many types of cell in the presence of anaesthetics, and enunciated a theory which stated that narcotics acted through a decreased permeability of the cell membrane. The action of a narcotic on cell permeability, however, varies from cell to cell and from species to species (Danielli, 1950).

Anaesthetics may interfere with the increase in permeability occurring during excitation, and thus resist depolarization. Resistance of the surface of peripheral nerve fibres to depolarization is produced by numerous drugs—local anaesthetics like cocaine and procaine (Bennett and Chinburg, 1946), and anticholinesterases such as physostigmine and dyflos (Toman, Woodbury and Woodbury, 1947)—and block from persistent depolarization is caused by ethanol and ether (Wright, 1947). But it is doubtful whether the results obtained from the easily accessible, peripheral nerve fibres also apply to the cells of the central nervous system: conduction in peripheral nerves, motor or sensory, is not abolished during general anaesthesia.

The undoubted ability of most anaesthetics to lower surface tension may account for their accumulation at the cell surface, and Warburg (1921) has suggested that anaesthetics thus adsorbed, probably by attachment to the surface lipoids, may displace certain respiratory enzymes essential for oxidative processes, and interfere with the permeability of the cell membrane. There is little doubt that many do act at the cell membrane (Hiller, 1927), for it has been shown that, if injected deep into the cell, certain anaesthetics are inactive, whereas they are effective when applied to the cell surface (Marsland, 1934) or, sometimes, when injected immediately beneath the surface.

Dehydration. It has been realized for some time that anaesthetics reduce the state of hydration of nerve and other cells. Dubois showed, seventy years ago, that high concentrations of anaesthetics led to water being exuded by plant cells; Kochmann (1923a) found that frog muscles decrease in weight when exposed to effective concentrations of anaesthetics; Jurisic (1937) demonstrated loss of water from fibrin in the presence of chloral hydrate; and Lapicque (1930) discovered that narcotics, in concentrations sufficient to depress conduction, reduce hydration of nervous tissue. These facts, and others, have led Seelich (1940) to suggest that anaesthesia may be the result of dehydration of brain cells, because of a change occurring in the cell surface leading to a diminished power to attract and hold water. The membrane change is considered to follow the solution of the anaesthetic in the surface lipoids. (Here, it is worth noting that Meyer and Overton never specified which lipoids were concerned in anaesthetic action so that the theory of Seelich may be regarded as an elaboration of their ideas.) When the anaesthetic dissolves in the lipoids of the cell membrane there is a rearrangement of the total lipoids of the cell. The hydrophilic lipoids, which were originally mainly on the surface and which now contain the anaesthetic, withdraw into the cell, and less hydrophilic lipoids of the cell interior take their place. The result is less attraction for water and

diminished ability to hold that already in the cell, leading to dehydration and an alteration in surface permeability.

Seelich has made some interesting observations on the interface of a liquid paraffin/water system. Ergosterin, dissolved in the liquid paraffin to represent the hydrophilic lipoid of the cell surface, enormously reduced the interface energy making it more like a lipoid/water system. The addition of certain strongly surface-active narcotics then had little effect on the already low surface energy: indeed it was sometimes raised. Such a rise in surface tension is accompanied by a decreased attraction for water, and leads to dehydration. The state of hydration of colloidal solutions, quite apart from cellular structures, is also decreased by many anaesthetics.

This dehydration theory of anaesthesia, first suggested in 1884 by Dubois, and later modified and extended by Kochmann (1923b), and Seelich (1941), has been emphasized by Burn and Epstein (1946) who consider that dehydration is one of the fundamental changes leading to anaesthesia.

An interesting point about this theory is that it allows an alternative explanation of the excitement that often occurs during the second stage. Although such excitement is usually said to be due to release of lower centres from cortical control, it is possible that low concentrations of anaesthetics may actually stimulate. Lapicque has described facilitation of conduction in nerve fibres by low concentrations of anaesthetics: he found that, in these conditions, there was increased hydration. If anaesthesia is assumed to be due to dehydration, then one would expect increased hydration to be accompanied by stimulation.

OBITER COGITATIONES

Ναρκωτικός means benumb or stupefy and, since the time of Galen (Butler, 1950), has been used to refer to soporific drugs. As opium is the most outstanding member of this class of drugs the properties of opium have come to be regarded as narcotic. Narcosis, however, is now used by pharmacologists and biologists to describe a reversible depression of the functions of a cell and so, when applied to the brain, means much the same as anaesthesia, which, in the words of Oliver Wendell Holmes, "signifies insensibility". So, throughout this discussion the terms anaesthesia and narcosis have been regarded as synonymous.

The first attempts to theorize about the mode of action of drugs were in connexion with the phenomena of anaesthesia. Although no satisfactory explanation of how anaesthetics act has so far been produced, the science and technique of anaesthesia have rapidly grown and progressed. Theories about the modes of action are not only of academic interest, however, for exact knowledge of the mechanism would probably lead to the discovery of better anaesthetic drugs.

The applicability to the brain of information obtained from experiments on peripheral nerves, isolated organs, or physical models remains very doubtful but, so far, these are the only experimental approaches to the problem. An adequate and satisfactory explanation of the mode of action of anaesthetics is not likely to be formulated until more is understood of the functioning of the brain.

REFERENCES

Bancroft, W. D., and Richter, G. H. (1931). *J. phys. Chem.*, **35**, 215.

Bennett, A. L., and Chinburg, K. G. (1946). *J. Pharmacol.*, **88**, 72.

Bernard, C. (1853). Cited by Sollmann, T. (1942). *A Manual of Pharmacology*, 7th Ed., p. 605. Philadelphia: Saunders.

—— (1875). *Leçons sur les anaesthésiques et sur l'asphyxie.* Paris: Baillière.

von Bibra., E., and Harless, E. (1847). *Die Wirkung des Schwefeläthers in Chemischer und Physiologischer Beziehung.* Erlangen (Cited by Burn and Epstein, 1946).

Burn, J. H., and Epstein, H. G. (1946). *Brit. med. J.*, **2**, 533.

Butler, T. C. (1950). *Pharmacol. Rev.*, **2**, 121.

Danielli, J. F. (1950). *Cell Physiology and Pharmacology*, p. 102. London: Elsevier.

Dubois, R. (1884). *C. R. Soc. Biol., Paris*, **36**, 582.

Ferguson, J. (1939). *Proc. roy. Soc. B.*, **127**, 387.

Hiller, S,. (1927). *Proc. Soc. exp. Biol., N.Y.*, **24**, 427, 938.

Höber, R. (1907). *Pflüg. Arch. ges. Physiol.*, **120**, 492.

—— (1945). *Physical Chemistry of Cells and Tissues.* London: Churchill.

Johnson, F. H., Brown, D. E. S., and Marsland, D. A. (1942). *J. cell. comp. Physiol.*, **20**, 269.

Jowett, M. (1938). *J. Physiol.*, **92**, 322.

—— and Quastel, J. H. (1937). *Biochem. J.*, **31**, 1101.

Jurisič, P. J. (1937). *Kolloidzschr.*, **78**, 95.

Keilin, D. (1925). *Proc. roy. Soc. B.*, **98**, 312.

Klein, J. R. (1943). *J. biol. Chem.*, **151**, 651.

Kochmann, M. (1923a). *Biochem. Z.*, **136**, 49.

—— (1923b). In *Heffter's Hdb. exp. Pharmak.*, **1**, 466.

Krantz, J. C., and Carr, C. J. (1954). *Pharmacologic Principles of Medical Practice*, 3rd Ed., p. 431. London: Baillière.

Lapicque, L. (1930). *Arch. int. Pharmacodyn.*, **38**, 209.

Lillie, R. S. (1909). *Amer. J. Physiol.*, **24**, 14.

Marsland, D. (1934). *J. cell. comp. Physiol.*, **4**, 9.

Meyer, H. H. (1899). *Arch. exp. Path. Pharmak.*, **42**, 109.

—— and Gottlieb, R. (1936). *Die. Experimentelle Pharmakologie*, 9th Ed., p. 821. Berlin: Urban und Schwarzenberg.

Meyer, K. H. (1937). *Trans. Faraday Soc.*, **33**, 1062.

—— and Hemmi, H. (1935). *Biochem. Z.*, **277**, 39. (Cited by Butler.)

Moore, B., and Roaf, H. E. (1904). *Proc. roy. Soc.*, **73**, 382.

—— —— (1905). *Proc. roy. Soc., B.*, **77**, 86.

Overton, E. (1901). *Studien über die Narkose.* Jena.

Quaştel, J. H., and Wheatley, A. H. M. (1933). *Biochem. J.*, **27**, 1609.

—— —— (1934). *Biochem. J.*, **28**, 1521.

Richet, C. (1893). *C.R. Soc. Biol., Paris*, **45**, 775.

Seelich, F. (1940). *Pflüg. Arch. ges. Physiol.*, **243**, 283.

—— (1941). *Ergebn. Physiol.*, **44**, 446. (Cited by Burn and Epstein, 1946).

Toman, J. E. P., Woodbury, J. W., and Woodbury, L. A. (1947). *J. Neurophysiol.*, **10**, 429.

Traube, J. (1904). *Pflüg. Arch. ges. Physiol.*, **105**, 541.

Verworn, M. (1909). *Dtsch. med. Wschr.*, **35**, 1593.

Warburg, O. (1921). *Biochem. Z.*, **119**, 134.

Wright, E. B. (1947). *Amer. J. Physiol.*, **148**, 174.

PLANNING A CLINICAL INVESTIGATION

BY

JOHN W. DUNDEE

Department of Anaesthesia, University of Liverpool

NEED FOR CLINICAL INVESTIGATION

BEECHER (1952) quotes an eminent clinician as stating, "I have used the remedy you sent me in several patients. It is my distinct impression that this is the finest thing ever made for the purpose." Remarks like this show the necessity for controlled clinical investigation of new drugs and the folly of placing too much reliance on clinical impressions.

Much can be done by laboratory studies in animals, and in fact no new drug is placed on the market until the essential facts as regards its toxicity, etc., are available. However, there is a large species variation in response to drugs and the results of animal experiments are not always applicable to man. As an example of this is the fact that 1/6 gr. (10 mg.) morphine will have about the same sedative action in a 10-kg. dog as in a 10-stone (63 kg.) man.

Anaesthetic techniques can be studied in animals and some of the associated hazards discovered, but it is impossible to do a controlled investigation into the benefits of a new technique on animals alone. Not only are the operative procedures to which animals can be subjected different from those performed in man, but we lack means of providing the concurrent pathology, and the habits of animals exclude the possibility of studying the sequelae of anaesthesia or carrying out a "follow-up". Only by controlled clinical investigation can we obtain the answers to the majority of problems which face anaesthetists.

Results obtained from an investigation are seldom so clear-cut as to leave no doubts regarding their interpretation.

In this paper it is proposed to discuss some of the difficulties that are encountered by the inexperienced when planning a clinical investigation. The various methods of statistical analysis are not described, but rather the means of obtaining results which can be subjected to such an analysis. The importance of proper planning of an investigation is stressed by Hill (1950) who says that "no statistical method can compensate for a badly planned experiment".

PREPARATION

"Without hypothesis there is no useful observation." This statement by Charles Darwin can be criticized on the ground that many discoveries in anaesthesia were made by chance. In answer to this we have Pasteur's remark that "in the field of experiment chance only favours the mind that is prepared."

"A mind that is prepared" is the first essential for any clinical investigation. Preparation can only result from a knowledge of the relevant literature. There are

no short cuts in obtaining this knowledge but unnecessary time can be lost by indiscriminate reading. The use of the *Index Medicus* and other classified lists of medical literature have been described by Lee (1954), who also gives advice as to the simplest and most efficient method of recording information. Review articles are becoming more common, and a search through *Physiological Reviews* or *Pharmacological Reviews* may be of benefit. If any study, other than of a purely clinical nature, is contemplated one is advised to consult *Methods in Medical Research*. These publications appear in several volumes and deal with such topics as measurement of oxygen consumption, plethysmography, gas flows, and manometric analysis. The literature issued by reputable drug firms is often helpful. On request most of these will supply additional information about their products to anyone intending to make a study of them.

As will be mentioned later the nature and objects of a clinical investigation often change somewhat as the study proceeds. Although one's knowledge of a subject may seem thorough at the beginning, as new lines of thought are opened up so there will be need for further reading, and the problems that crop up during the course of an investigation call for the same sustained search of the literature. Increased interest in a topic always occurs once one has started on an actual investigation.

PRECONCEIVED IDEAS

While a preliminary plan of an investigation is an essential, one must be prepared to revise it as the work proceeds. It is rare to complete any study and finish up only with the answers one set out to find. Many things alter the course of an investigation and probably the first will be the difficulties in the techniques involved. Once the study gets under way it may be found that its original plan was too ambitious and could not be carried out with the staff and time available. The routine pre- and post-operative treatment of the patient may also have a bearing on the course of the investigation; e.g., a study of the effect of anaesthetic agents on the electrolytes will be affected by the incidence of blood transfusions. In most cases this sort of difficulty can be foreseen when planning the experiment but occcasionally it may be overlooked until the study gets under way. In this respect it must be stressed again that the welfare of the patient must always take priority over the investigation; any other code would be highly unethical.

Some important points in the published literature may come to light during an investigation and alter its form completely. One may even find that the work has been done before, but this should not stop the study, as confirmatory evidence of any published results is always valuable. One may even find results at variance with those in the literature and thus open up another line of investigation.

It is advisable to review the object and plan of an investigation once sufficient results are available to give an idea of its progress. At this review one must again be prepared to change the nature of the work, or bring emphasis to bear on another aspect of it. The importance of recording all data, whether apparently relevant or not, until such a review has taken place will be stressed later.

CONTROLS

In discussing "Pain and some factors that modify it", Beecher (1951) remarks: "One of the greatest problems in the study of pain is the discovery and control of dependable yardsticks." This applies equally well to any clinical study. It is not sufficient to conclude that a particular anaesthetic technique is a good one, or that a new drug gives satisfactory results. To be of any value at all, one must find how the technique compares with those in current use, or how the drug stands in relation to the standard member of the same group of drugs. Of topical interest are the French publications on "Artificial Hibernation" which many workers claim to be a major advance in anaesthesia. However, as yet no one has published a series of cases comparing results with this technique—not only in regard to the condition of the patient during operation, but also in the post-operative period—with orthodox techniques used by the same workers, on a comparable series of cases.

The ideal method of obtaining control readings is for patients to act as their own controls. Unfortunately, this can only apply to such experiments as those designed for comparing analgesic drugs. Even in this field, the scheme of administering and withholding a drug alternately to the same patient is not altogether satisfactory, as the mere fact of having a tablet or injection has a psychological effect which will undoubtedly have some influence on the patient's response to pain. One has to resort to the use of placebos which cannot be distinguished by the patient from the active drug. To ensure uniformity in interpretation of results it is also advisable that the observer is not aware when the active drug or placebo has been given. For a full discussion of the problem of placebo-reactors and non-reactors the reader is referred to the publications on this subject by Beecher (1953) and Beecher, Keats, Mosteller and Lasagna (1953).

The next best thing to having patients act as their own controls is to collect two large comparable series of cases in which the only difference is the point under observation, whether this be an anaesthetic technique or a drug. New relaxants can be compared with d-tubocurarine chloride, new ultra-rapid-acting barbiturates with thiopentone, new intravenous analgesic supplements with pethidine, etc. In any two series one has to act on the assumption that each is representative of the population from which it is drawn. There can therefore be no selection of patients. Thus the simplest method of obtaining a comparable series is to use alternate cases as controls. Here again the individual factor of interpretation of findings comes into the picture, and the one person must be concerned with equal numbers of comparable cases from each series.

In comparing the effect (or dosage) of different drugs in two series of cases, factors such as the nature and duration of operation, body weight, sex and age have to be considered in balancing the series. As an example of this is the observation by the author that the requirements of thiopentone vary with age, sex and body weight (Dundee, 1954a), while these factors are unimportant in the case of tubocurarine chloride and laudexium (Dundee, 1954b). Often factors are involved which appear to have no relation to the problem; for example, the effect on

blood pressure may be the main factor in the action of a drug on liver function after operation. To compare two drugs as regards their hepatic toxicity and not know the incidence and duration of hypotension in each series is useless. Another example is the influence of a new agent in causing post-operative respiratory complications. To combine this agent with a relaxant which is not completely reversed before return to the ward and compare the sequelae to nitrous oxide-oxygen-ether would be bound to result in a fallacious conclusion.

As regards the size of the series the answer is to have it as large as possible. The larger the number of cases the greater is the probability of each series being representative of the population from which it is drawn. The minimum number will depend upon the findings. In general, the smaller the difference, the more cases needed. One may get a 30 per cent incidence of respiratory complications after technique A, and 20 per cent after technique B at the end of 10 cases with each technique. However, after 50 cases of each the figure may be 60 per cent and 10 per cent respectively, or alternatively 50 per cent of each.

In reading anaesthetic literature one discovers equally good results claimed for spinal anaesthesia and various combinations of general anaesthesia with or without relaxants. The inference from this is that the anaesthetist himself is an important factor in the results obtained with any drug or combination of drugs. This has been mentioned already, when referring to balancing control and unknown series of cases in regard to administrators. There appear in the literature sets of figures, including complete details of cases from which they were obtained. One might be tempted to use such figures as controls for comparison with those obtained in the investigation, but this is rarely justified. As an example the author (Dundee, 1952a) published average requirements of d-tubocurarine chloride in 100 abdominal cases using controlled respiration. Later these figures were taken as controls for dosage of laudexium in a comparable series of cases (Dundee, Gray and Riding, 1954). This was only justified because the administrators in the two series were the same; should other workers have made this comparison the results would have been fallacious.

The extent to which one uses published figures for comparison with the results of an investigation depends on how much each series is influenced by the administrator. Such things as the incidence of a skin rash after di-ethyl ether would seem obviously unrelated to the person administering the anaesthetic (provided other factors are comparable) and published figures can be used as controls. There is no hard and fast rule about this and each set of circumstances must be considered on its merits.

Such is the importance of controls and "yardsticks of normality" that, when one is planning an investigation, it is a help to start collecting control readings. Time is saved during the actual investigation and some snags in the procedures involved may be brought to light. The figures obtained may later be discarded if such things as the weather are found to influence the findings, but the investigator has acquainted himself with the method of observation and recording of results.

REDUCTION OF VARIABLES

Methods of statistical analysis in current use generally deal with one unknown, and it is obvious that variables in any series must be reduced as much as possible. The effects of variation due to sex, age and weight of the patients have been discussed already. The effects and sequelae of operations depend to a large extent on their nature and duration. Furthermore there is different concurrent pathology in patients having different operations. As these factors may influence the results obtained from clinical investigations it is advisable to limit the cases to those of one age group and one type of operation. Patients with pre-operative pathology unassociated with the nature of their operation should not be used. As an example of this, if one is studying the effects of a ganglion blocking drug in producing postural ischaemia, or comparing the effects of two such drugs, care must be taken to see that cases undergoing thoraco-lumbar sympathectomy are not included with those for repair of herniae. Similarly in the study of post-operative respiratory complications, patients with upper abdominal incisions require separate consideration from non-abdominal cases.

Variables in the making of observations are easy to eliminate. The same team of observers must participate the whole investigation or the results will be meaningless. Different anaesthetists and surgeons may even vary in their interpretation of the term " satisfactory abdominal relaxation ".

As regards biochemical and haematological data one has often to assume that results from the same laboratory are always comparable. The fewer technicians engaged in any particular study the less will be the variation in this respect. It is obvious that samples for examination should be collected at the same time of day and that the time between taking the sample and the examination of it should be standard throughout the investigation.

A good illustration of the reduction in variables in clinical investigations is the report by Gillespie (1951) on the relation of intubation to post-operative respiratory complications. This was not a planned study, but rather an examination of record cards for the period 1940-1950. From the original 54,819 cards, by process of elimination he found 185 comparable cases in which the only variable was the presence or absence of an endotracheal tube. The steps in the elimination were:

(*a*) Total number of records examined ...	54,819
(*b*) Abdominal operations	8,316
(*c*) Number of (*b*) belonging to one physical state	3,581
(*d*) The largest single operation group	569
(*e*) The most commonly used anaesthetic ...	329
(*f*) One anaesthetic technique	211
(*g*) Exclusion of cases with pre-existing respiratory disease	185

RECORDING OF FINDINGS

It is of paramount importance, especially in the early stages of an investigation, that as much data as possible be recorded about patients. Seemingly irrelevant data may be necessary later to find if more than one variable has crept into a series of observations. Results obtained may well change the nature of an investigation so that apparently irrelevant data become of major importance. If such information is not available for all patients a large amount of work may be wasted and time lost.

The above points can be illustrated by the hypothetical example of an investigation of post-operative chest complications following the use of analgesic drugs A and B during a series of patients undergoing repair of herniae. All cases with pre-existing respiratory infection are excluded. Premedication is standard for all cases, the anaesthetic techniques only vary in respect as to whether supplement A or B was used, the same anaesthetist is responsible for cases, and patients undergoing only operations lasting between 45 and 75 minutes are followed up. With a constant method of observation one finds that after 25 cases in each series the incidence of respiratory complications following A is 10 per cent while the figure with B is 65 per cent. After this number of cases the ward sister mentions that she has noticed a recent high incidence of sickness in patients who have had herniae repaired. One immediately wonders if this is related to the incidence of chest complications. If data concerning post-operative vomiting are available they may reveal that analgesic A has a marked emetic action and that the movement and straining which accompanies the vomiting is the cause of the lower incidence of respiratory complications when this drug has been used. In the absence of this information the results of the investigation to date have lost their significance, for it is obvious that the line of research may change to a comparison of the emetic properties of the two drugs in question.

Statistical methods of analysis of data require that the facts be available as (*a*) a percentage of cases that show or fail to show the response looked for, as in the above example, or (*b*) figures from which an average can be calculated with variance from that average. This latter applies particularly to doses of drugs or such things as the time after operation when the first dose of analgesic drug was administered.

By using a points system it is often possible to record data which might seemingly come under (*a*) in actual figures. To return to the hypothetic example already referred to, instead of noting the absence or presence of respiratory complications one may proceed as follows:

1 point: slight cough for 24 hours
2 points: slight cough and sputum for 24 hours
3 points: slight cough for 48 hours
4 points: slight cough and sputum for 48 hours
5 points: slight cough and pyrexia over 100°F for 24 hours, etc.

A scheme can be worked out by allotting, say, 20 points to massive collapse and filling in all other possibilities in descending order of severity. The results may then become something like:

with analgesic agent A, average of 3.6 ± 0.5
with analgesic agent B, average of 10.8 ± 1.3

As can be seen, the points system is of value when recording the presence or absence of a factor which may be present to varying degrees. The author has found it to be particularly useful in recording the degree of shivering after the application of ice bags, in order to test the efficiency of various drugs in suppressing this reaction.

In two series of cases when the numbers of times that a response is present are being compared, the "chi-squared" method of analysis will be employed; whereas, when the averages of readings are under consideration, e.g. average temperatures or blood pressures, the "standard error of difference between two means" or

"T-test" must be used. Details of these can be found in *Principles of Medical Statistics* (Hill, 1950) or *An Introduction to the Theory of Statistics* (Yule and Kendall, 1947). Morton (1949) has recently drawn attention to these methods with particular reference to anaesthetic problems.

The system one adopts for recording data depends on personal preference, but two types of anaesthetic record cards in use can be adapted to suit most investigations. With the Nosworthy type there are sufficient spare holes along the bottom of the card to allow a personal recording system to be evolved. The Cardiff card, on the other hand, allows more space for post- and pre-operative data (Mushin, Lewis-Fanning and Morgan, 1954). Where minute-to-minute observations are required for a short period of time followed by less frequent observations, neither of these record cards are completely satisfactory. It is a simple matter to design a slip of paper for recording the special observations being made and attach this to the record card in current use at the hospital concerned. Some workers may prefer to make out their own record for all observations and not use either of the above systems. However, this should not be done to the detriment of the hospital record system, and if necessary both personal and routine records should be completed.

ILLUSTRATION

Many of the points mentioned above can be illustrated from the investigation into the role of thiopentone in the production of post-operative hepatic dysfunction, which appears on page 14 of this issue. In order to present a clear picture a few points will be discussed which do not appear in the original paper.

Preparation. The literature on the effects of thiopentone on liver function is shown to be extremely controversial, and in no published work is the effect of the drug differentiated from those of the operation.

Preconceived ideas. The original idea was to discover if liver dysfunction followed the use of thiopentone in man. This was to confirm a previous finding (Dundee, 1952b) that the liver plays a major role in the breakdown of thiopentone. The effect of thiopentone on liver function could only be investigated in volunteers who received varying doses of the drug, without any operative procedure to complicate matters. The information obtained from such a study was not considered of great enough importance to justify this. Accordingly use had to be made of patients who were receiving the drug for some operative procedure, and the nature of the investigation changed to finding the effects of various doses of thiopentone on liver function.

Of the various tests available the estimation of urinary urobilinogen excretion was the one which caused the least disturbance to the patient. Unfortunately the collection of the entire 24-hour output of urine presented difficulties from the nursing point of view and proved impossible on a large number of patients. The plan had to be simplified and only one daily specimen of urine, voided as near as possible to a fixed time after operation, was collected. This meant a diminution in the accuracy of the test as an index of liver dysfunction, and it was hoped to over-

come this by collecting a very large series of cases.

Of all the operative procedures for which one is asked to administer thiopentone, dilatation of the cervix and uterine curettage was likely to cause the least possible upset to the patient and seemed ideal for such a study. Furthermore, it can be carried out under many types of anaesthesia without disadvantage to the surgeon or patient. The first 150 cases in this investigation were with this operation, when the literature on "post-operative latent jaundice" came to my notice. This again altered the plan somewhat and operations at which a more marked extravasation of blood took place were included.

Controls. Unless it were possible to collect a series of patients who were operated on without any anaesthetic it is obvious that a "control series" was impossible. However, this was overcome by anaesthetizing alternate patients with (*a*) thiopentone used for induction of anaesthesia only and (*b*) thiopentone as the main narcotic. Near the end of the investigation the alternate case arrangement had to be abandoned so as to balance the series with each technique as regards sex and age. Equal numbers of cases for each operation of comparable duration were anaesthetized with each technique. Since the majority of anaesthetics were given personally or under personal supervision, the question of balancing the series as regards administrators did not present any difficulties.

Reduction of variables. Variables in the patients have already been discussed. The fact that patients had the same operation does not mean the same sequelae as regards liver dysfunction, and to correct this all factors such as hypotension during operation or a stormy convalescence excluded cases from the series. Post-operative sedation was considered a possible variable, but since all cases of any one operation were from the same hospital ward with the one doctor in charge it was hoped that sedation would be fairly standard.

Examination of urine was carried out by two people only during the whole series. Ideally both should have done the estimations independently and compared results, but this was not always possible. When this was done there was always agreement on the interpretation of the tests by both workers. The time between collection of specimens and examination was never more than one hour and this eliminated another variable factor.

Recording of results. During the operation, as well as recording the dose of thiopentone, the blood pressure, respiratory rate, etc., were noted. Although this data was not subsequently used in the investigation, it was as a result of this that many cases were excluded. The same applied to post-operative complications. Since the urobilinogen excretion does not give an idea of the degree of hepatic dysfunction, a points system of recording was not used. Two alternative interpretations of an abnormal excretion were noted, and since the final figures referred to the number of patients (or percentage) showing the presence or absence of excessive excretion of urobilinogen after operation, the "chi-squared" method of statistical analysis was used.

SUMMARY

Some of the problems associated with the planning of a clinical investigation are

discussed. Attention is drawn to the necessity of having results which can be subjected to statistical analysis. Many of the points raised have been illustrated by reference to published or hypothetical investigations.

REFERENCES

Beecher, H. K. (1951). *Anesthesiology*, **12**, 633.
—— (1952). *J. Amer. med. Ass.*, **151**, 44.
—— (1953). *J. Pharmacol.*, **108**, 158.
—— Keats, A. S., Mosteller, F., and Lasagna, L. (1953). *J. Pharmacol.*, **109**, 393.
Dundee, J. W. (1952a). *Brit. med. J.*, **2**, 893.
—— (1952b). *Brit. J. Anaesth.*, **24**, 81.
—— (1954a). *Brit. J. Anaesth.*, **26**, 164.
—— (1954b). *Brit. J. Anaesth.*, **26**, 174.
—— Gray, T. C., and Riding, J. E. (1954). *Brit. J. Anaesth.*, **26**, 13.
Gillespie, N. A. (1951). *Anaesthesia*, **6**, 206.
Hill, A. B. (1950). *Principles of Medical Statistics*, 5th Ed., London: Lancet.
Lee, W. A. (1954). *Brit. J. Anaesth.*, **26**, 389.
Morton, H. J. V. (1949). *Anaesthesia*, **4**, 100.
Mushin, W. W., Lewis-Fanning, E., and Morgan, J. H. (1954). *Brit. J. Anaesth.*, **26**, 298.
Methods in Medical Research, Chicago: The Year Book Publishers.
Yule, G. U., and Kendall, M. G. (1947). *An Introduction to the Theory of Statistics*, 13th Ed., London: Griffin & Co.

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